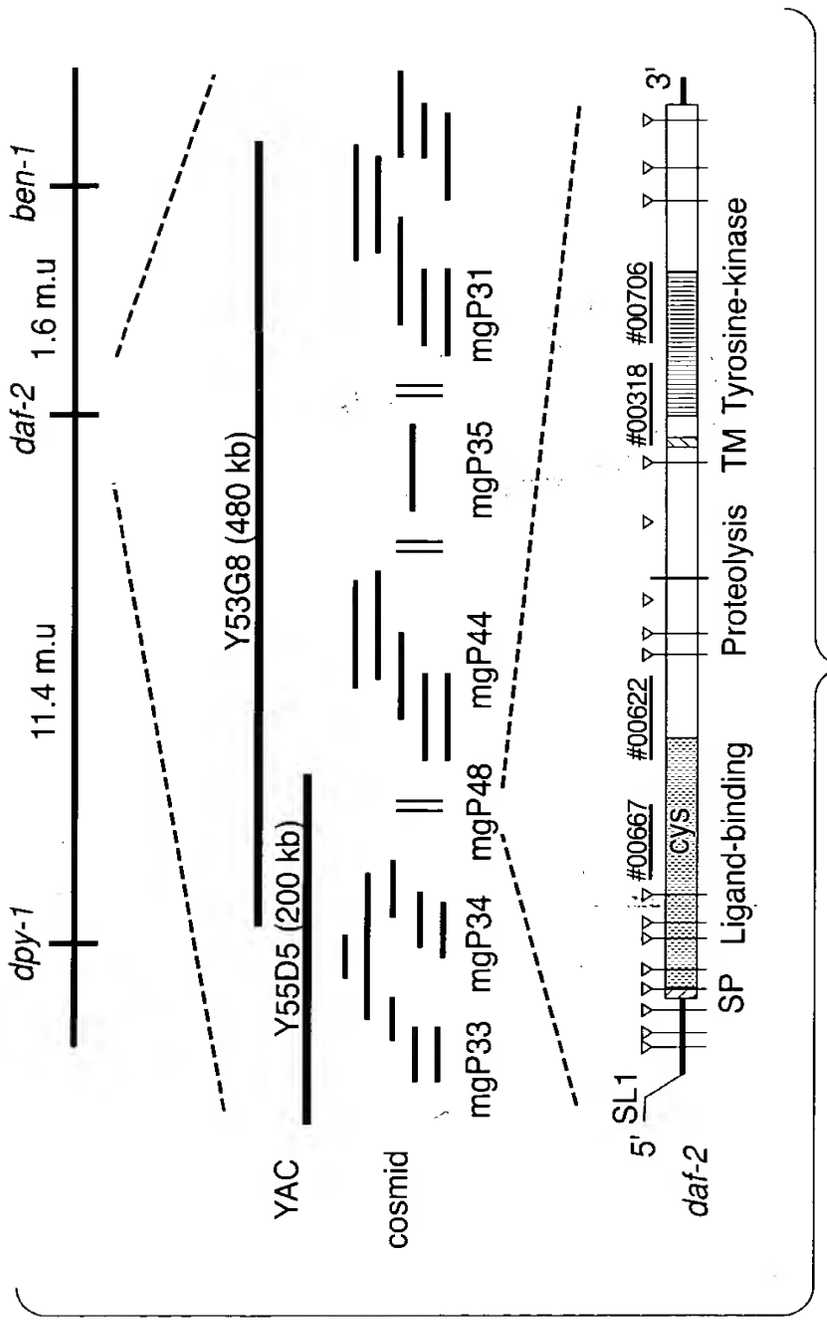

Fig. 1

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 541 VFFSWPSFNITDIDQRKFLGYELFFKEVPRIDENMTIEEDRSACVDSWQSVFKQYYETSN
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Fig. 2A

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Fig. 2B (sheet 1 of 3)

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Fig. 2B (sheet 2 of 3)

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Fig. 2B (sheet 3 of 3)

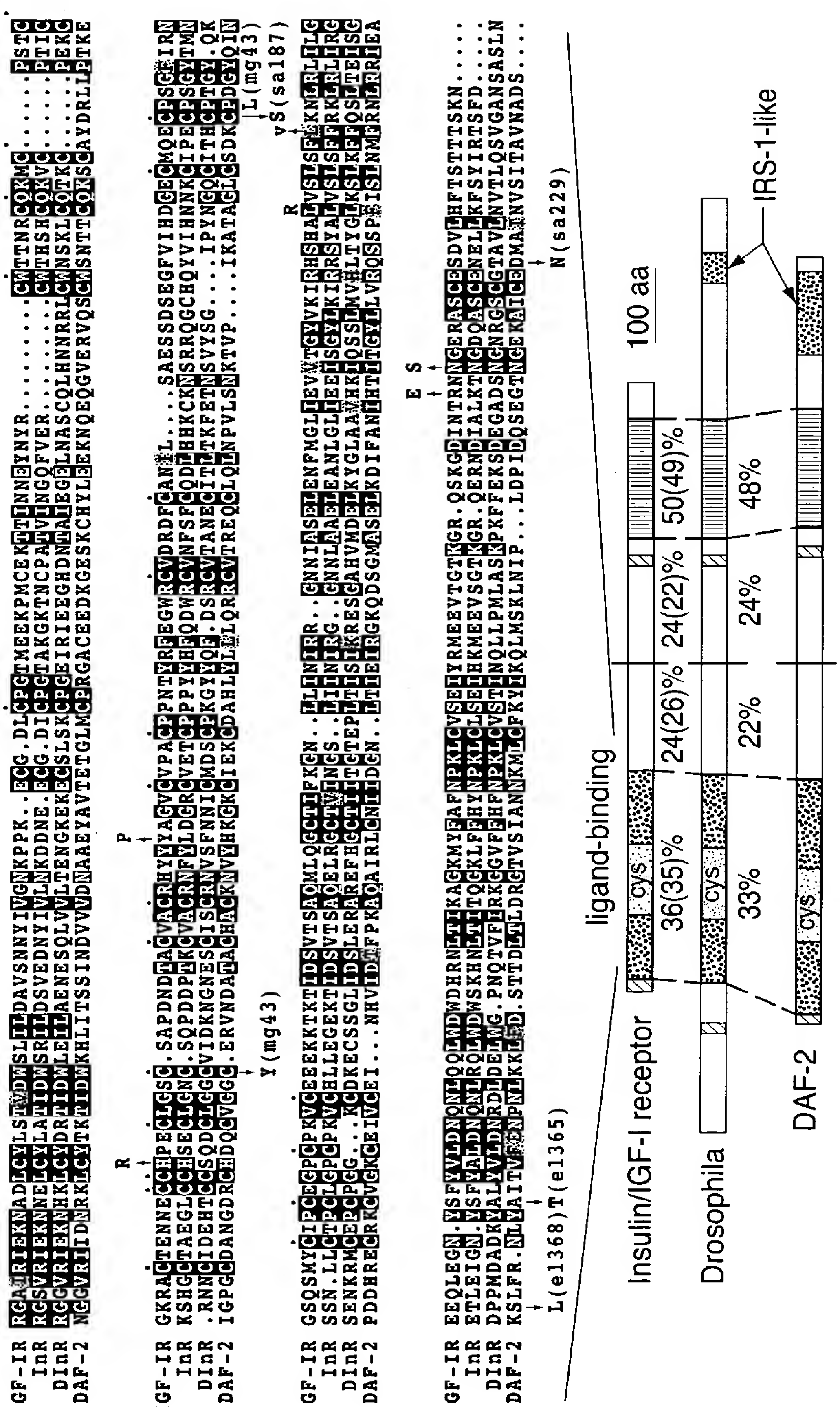


Fig. 2C (sheet 1 of 2)

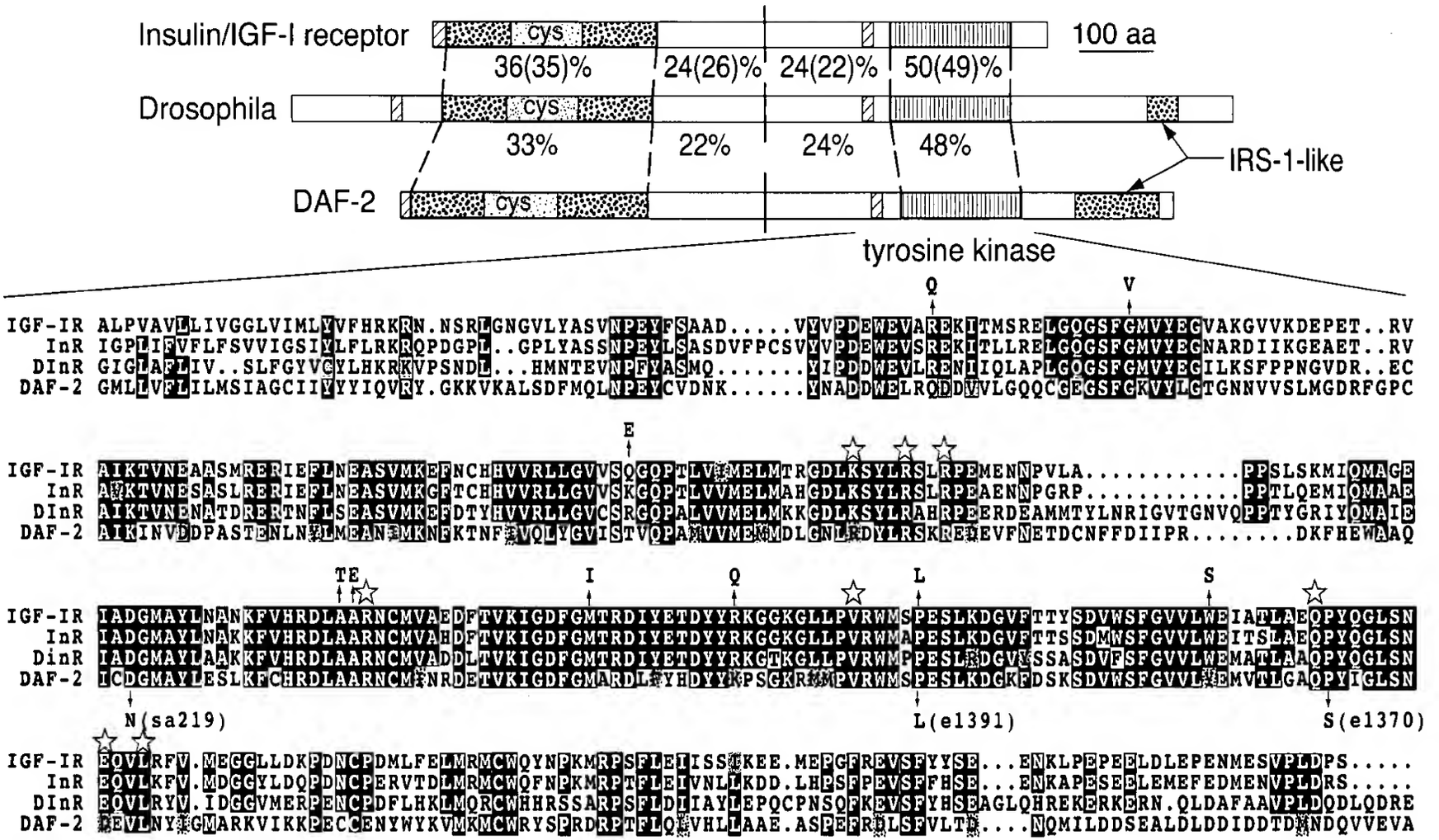


Fig. 2C (sheet 2 of 2)

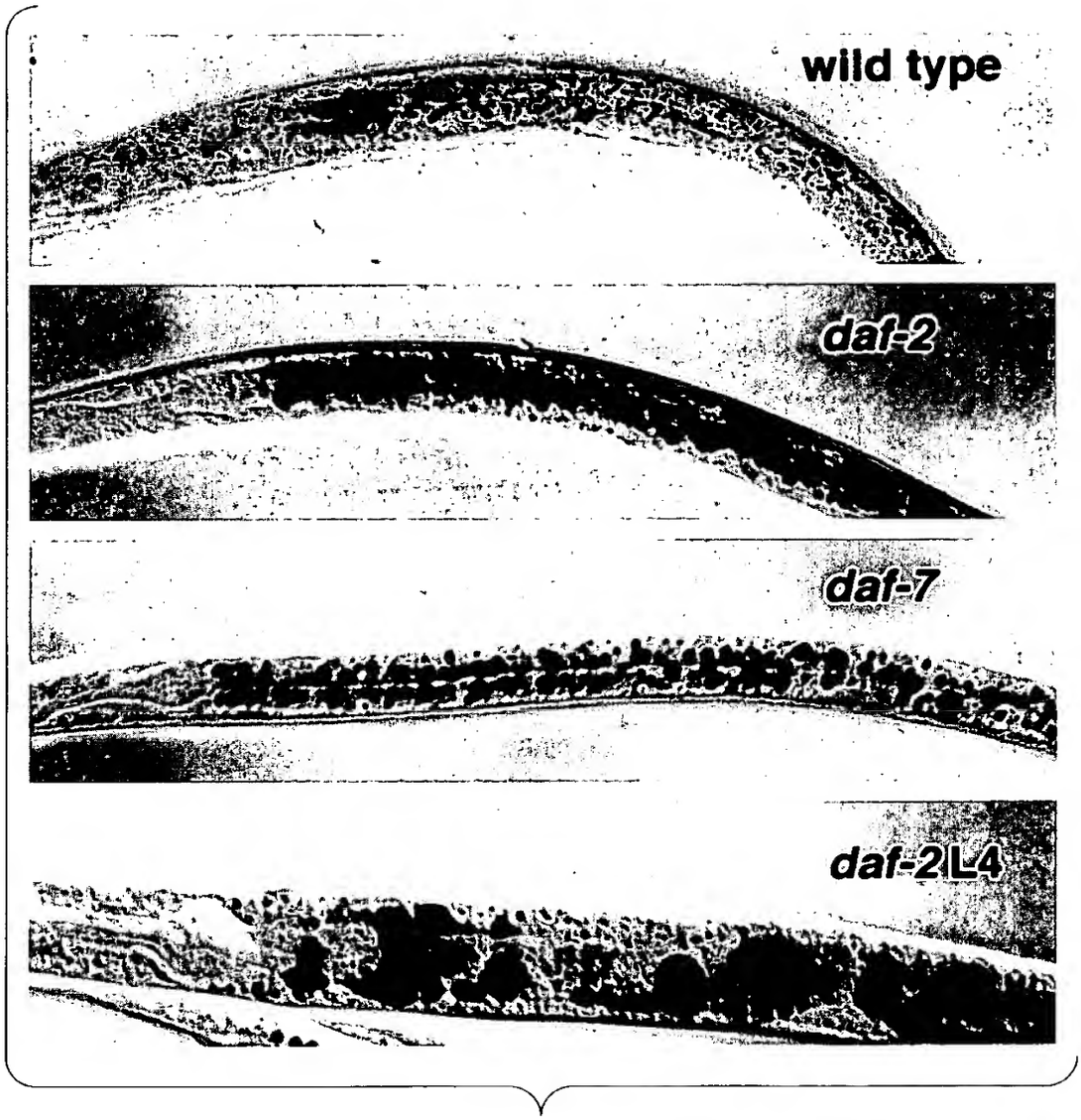
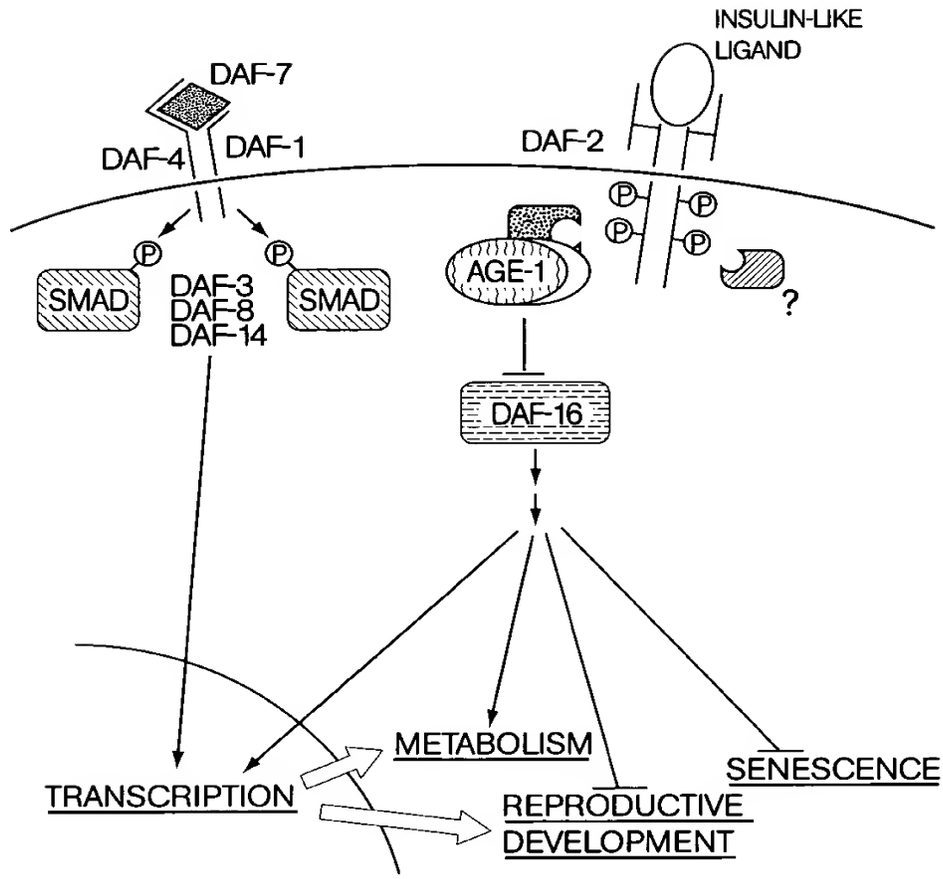


Fig. 3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P
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METABOLISM
SENESCENCE
TRANSCRIPTION
REPRODUCTIVE
DEVELOPMENT

Fig. 4

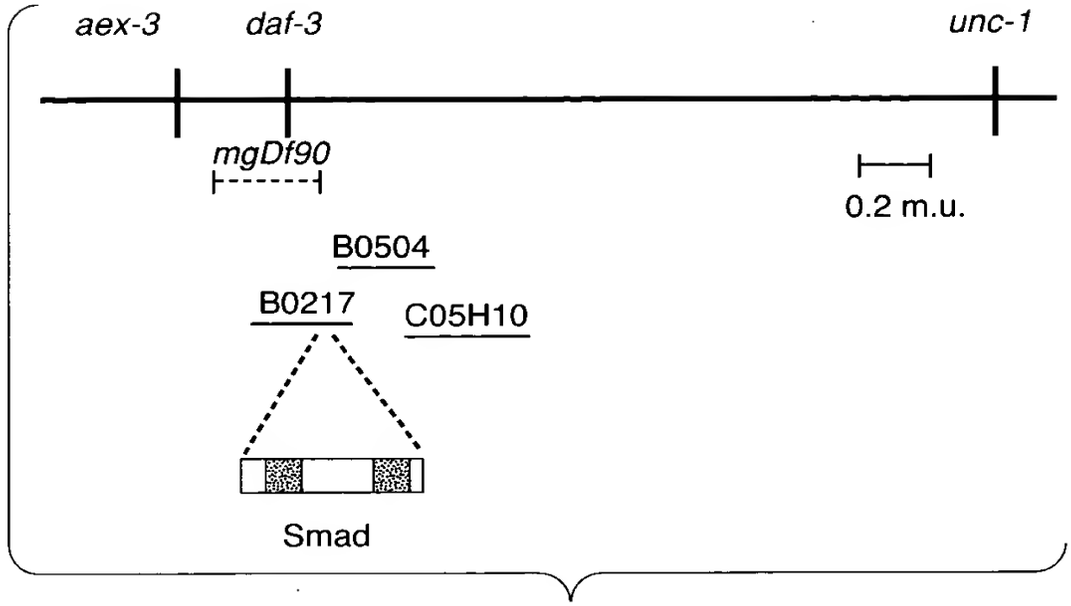
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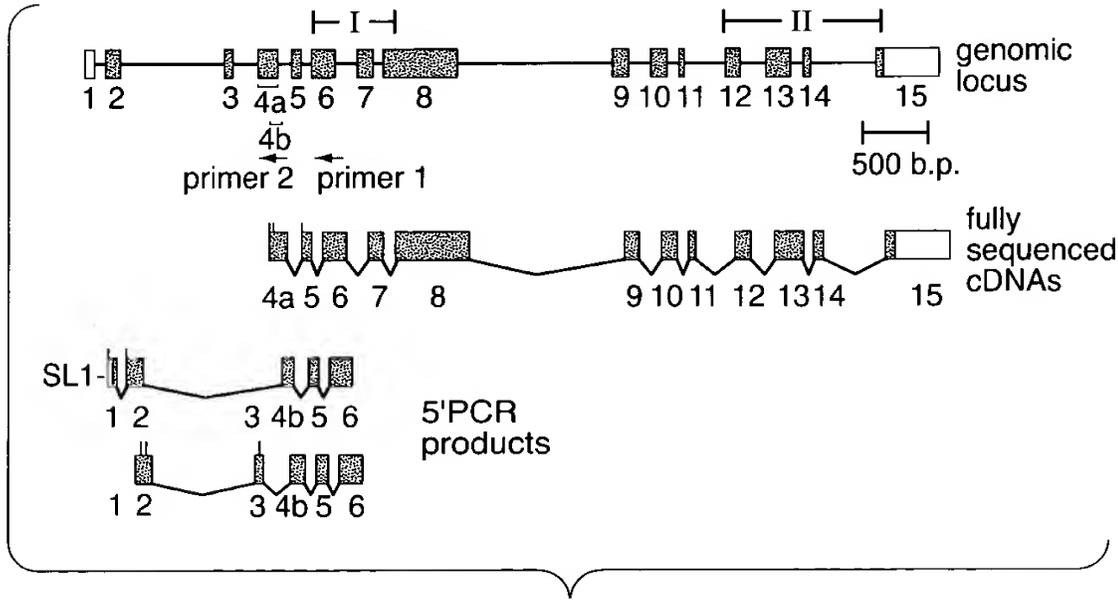
Fig. 5A


I
II
genomic locus
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primer 2
primer 1
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fully sequenced cDNAs
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SL1-
1 2 3 4b 5 6
5'PCR products
1 2 3 4b 5 6

Fig. 5B


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DPC4 GGESETFAKRAIESLVKKLKEKKDELDSLITAITTNGAHPSKCVTIQRTLDG
mg125 P->L
RLQVHGRKGFPHVVYGKLWRFNEMTKNETRHVDHCKHAFEMKSDMVCVNPYH
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Domain II
DAF-3 IVYYEKNLQIGE..KKCSRGNFHVDGGFI..CSENRYSLGLEPNPIREPVAFKV
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Fig. 5C

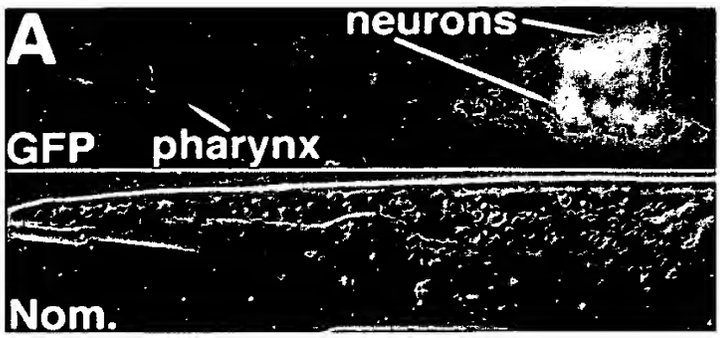
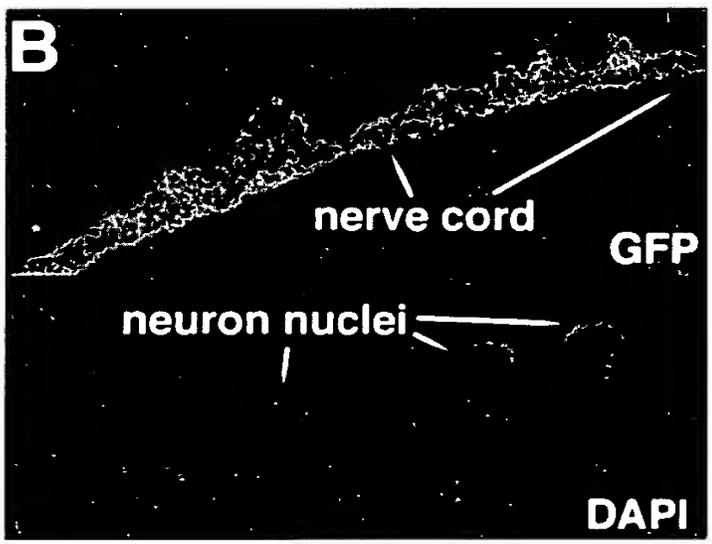


Fig. 6A



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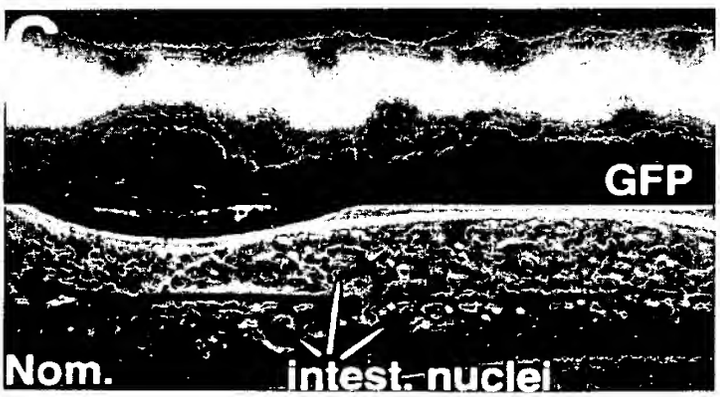
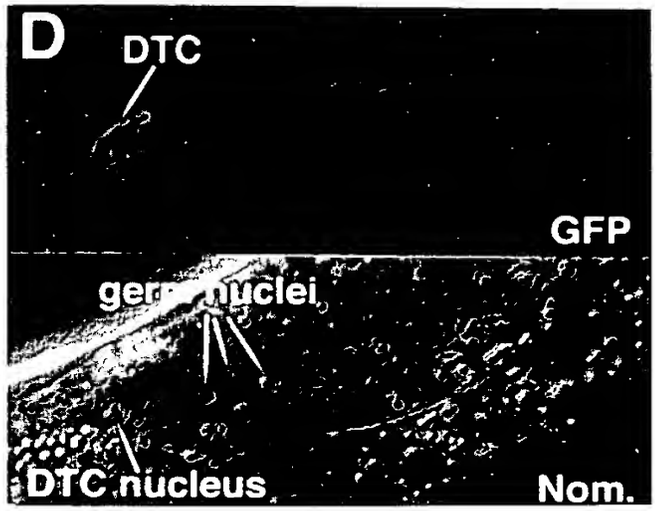


Fig. 6C



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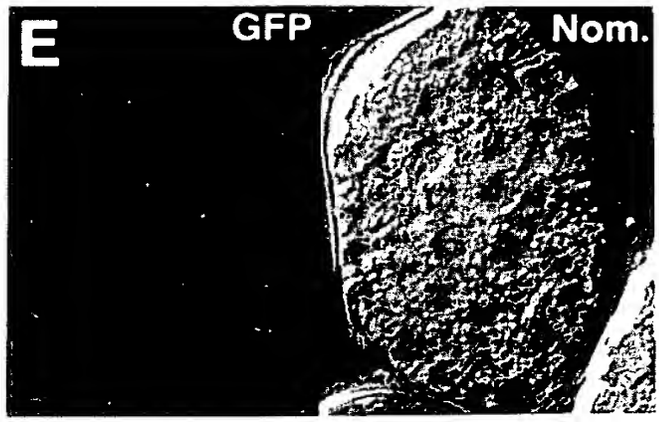


Fig. 6E

Fig. 6F

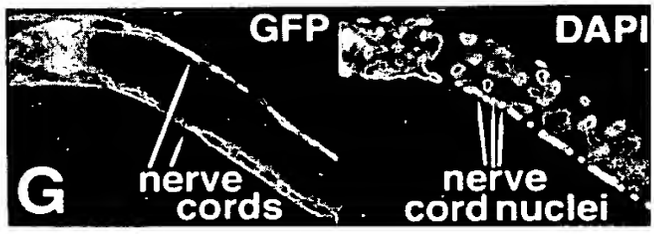


Fig. 6G

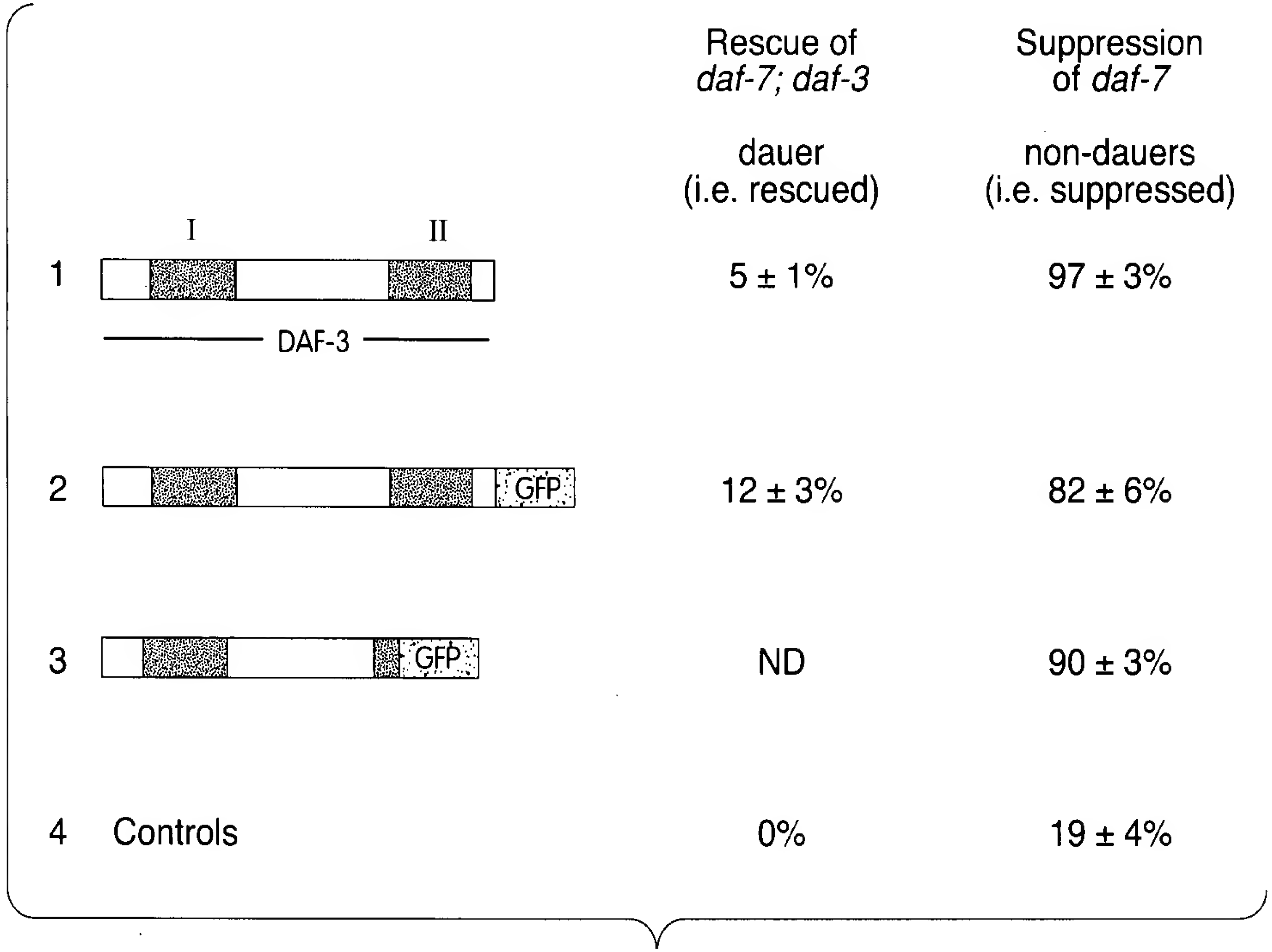
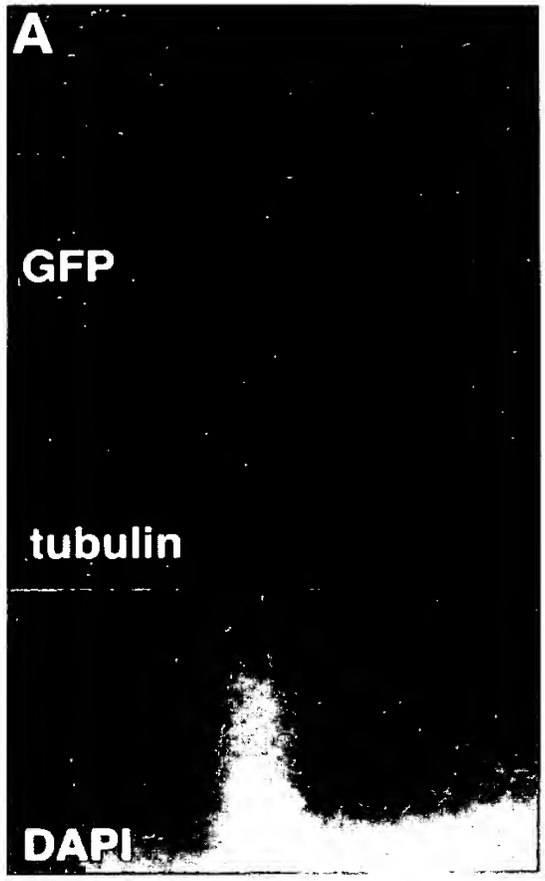


Fig. 7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GFP
tubulin
DAPI

Fig. 8A

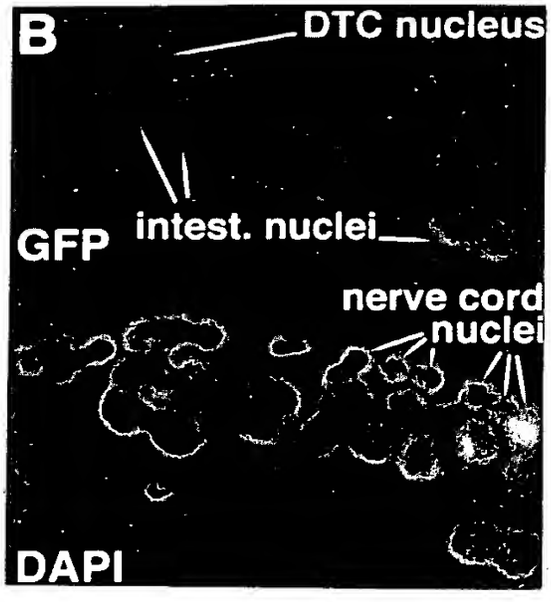
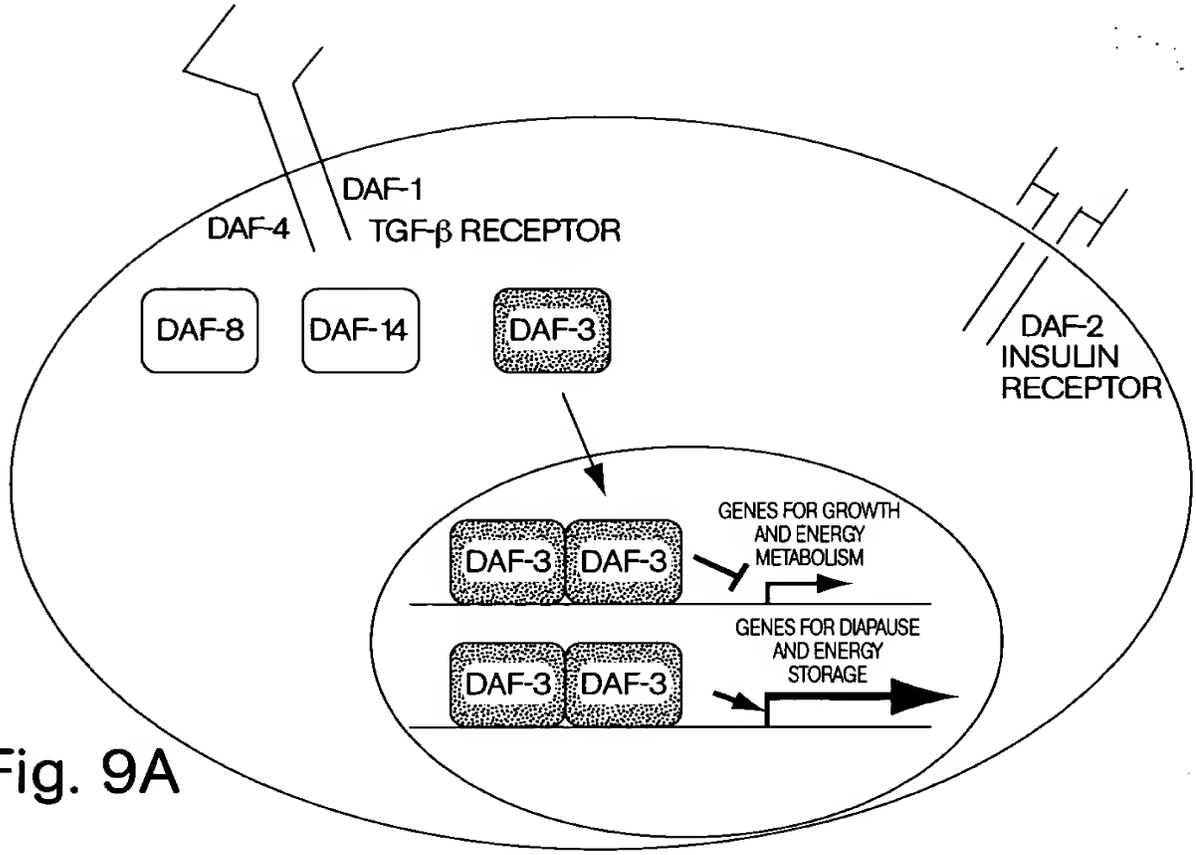

B
DTC nucleus
intest. nuclei
GFP
nerve cord nuclei
DAPI

Fig. 8B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DAF-4
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DAF-3
GENES FOR GROWTH
AND ENERGY
METABOLISM
DAF-3
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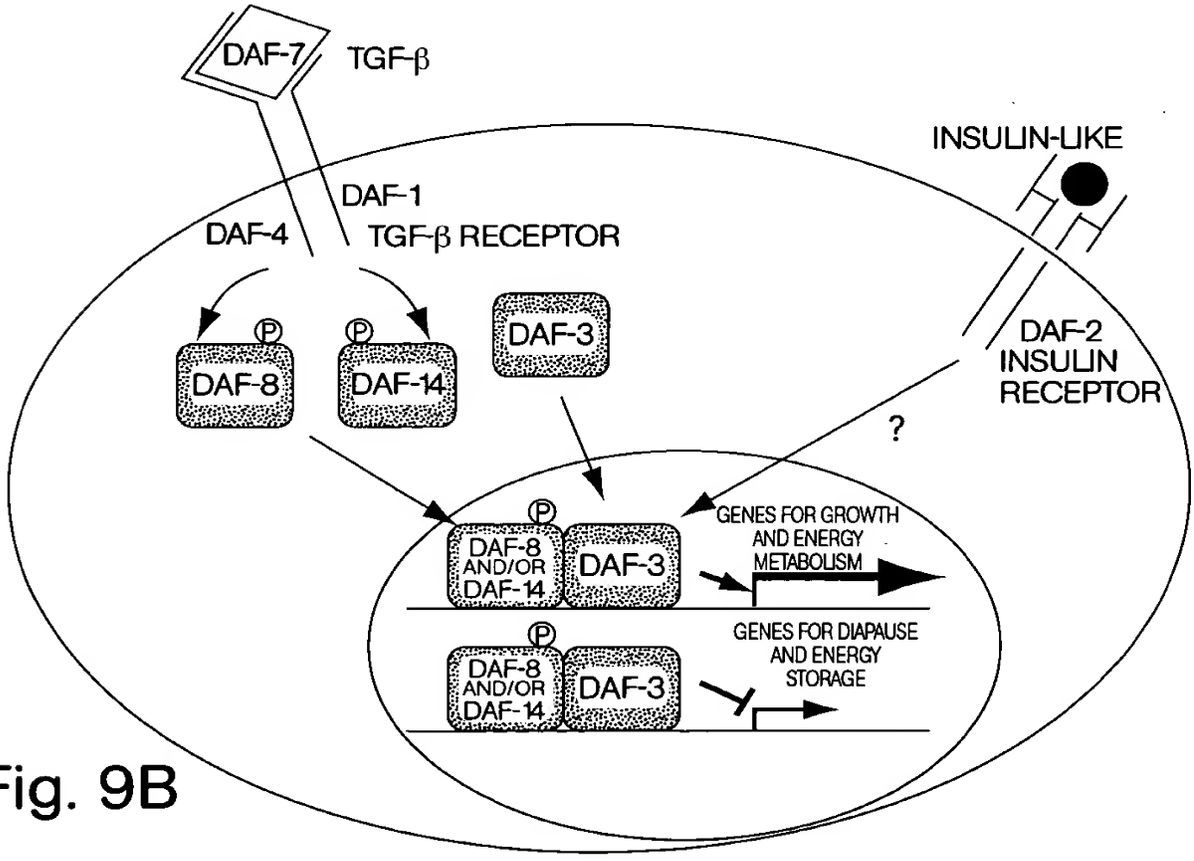
GENES FOR DIAPAUSE
AND ENERGY
STORAGE

Fig. 9A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P
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DAF-2
INSULIN
RECEPTOR
?
P
DAF-8
AND/OR
DAF-14
DAF-3
GENES FOR GROWTH
AND ENERGY
METABOLISM
P
DAF-8
AND/OR
DAF-14
DAF-3
GENES FOR DIAPAUSE
AND ENERGY
STORAGE

Fig. 9B

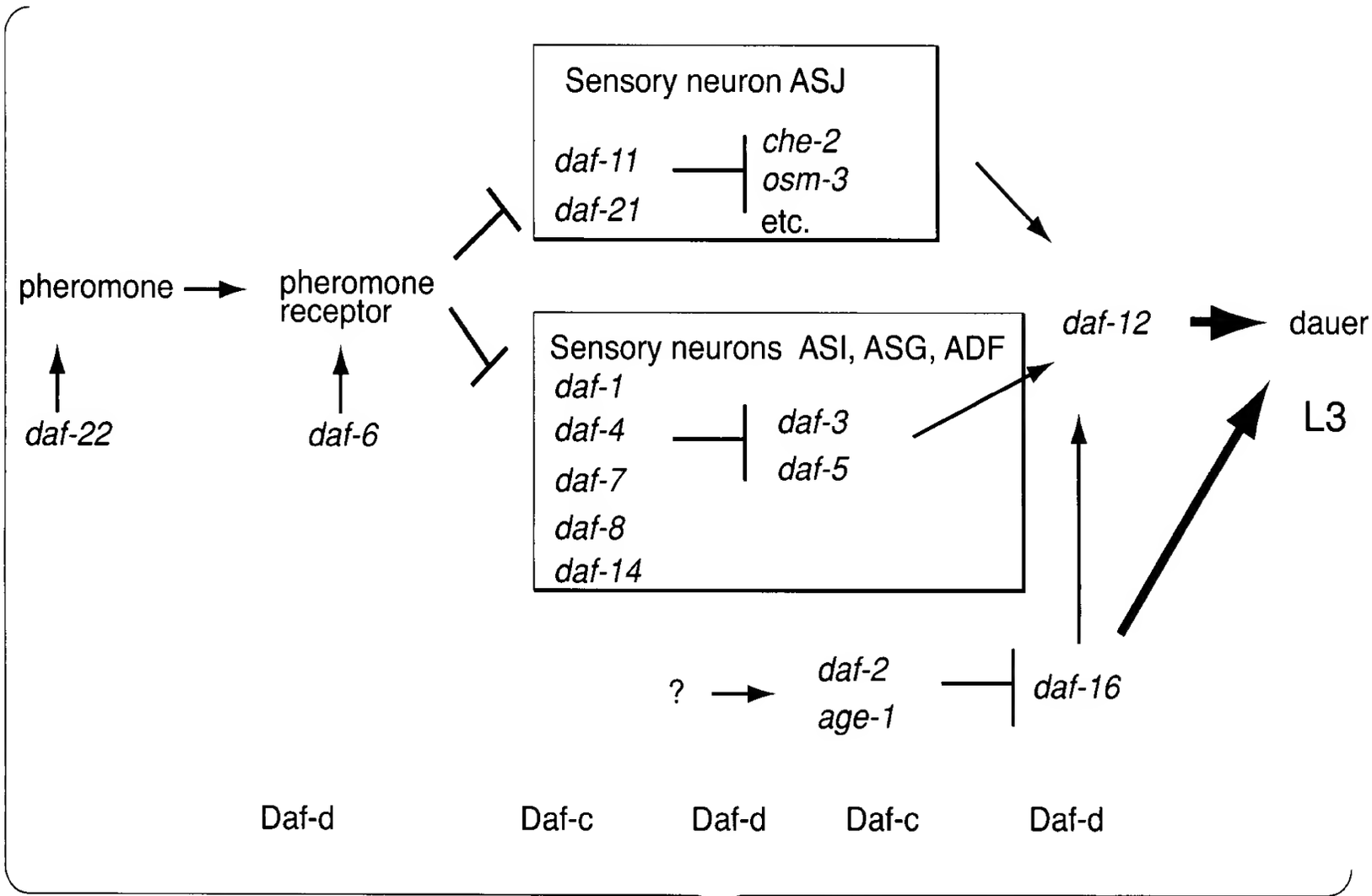

Fig. 10

```
   1  atgaagctaa tagcaacttc tcttctagtt cccgacgagc acacaccgat
  51  gatgtcacca gtgaatacaa ctacaaagat tctacaacgg agtggtatta
 101  aaatggaaat cccgccatat ttggatccag acagtcagga tgatgacccg
 151  gaagatggtg tcaactaccc ggatccagat ttatttgaca caaaaaacac
 201  aaatatgacc gagtacgatt tggatgtgtt gaagcttgga aaaccagcag
 251  tagatgaagc acggaaaaag atcgaagttc ccgacgctag tgcgccgcca
 301  aacaaaattg tagaatattt gatgtattat agaacgttaa aagaaagtga
 351  actcatacaa ctgaatgcgt atcggacaaa acgaaatcga ttatcgttga
 401  acttggtcaa aaacaatatt gatcgagagt tcgaccaaaa agcttgcgag
 451  tccctggtga aaaaattgaa ggataagaag aatgatctcc agaacctgat
 501  tgatgtggtt ctttcaaaag gtacaaaata taccggttgc attacaattc
 551  caaggacact tgatggccgg ttacaggtcc acggaagaaa aggtttccct
 601  cacgtagtct atggcaaact gtggaggttt aatgaaatga caaaaaacga
 651  aacgcgtcat gtggaccact gcaagcacgc atttgaaatg aaaagtgaca
 701  tggtatgcgt gaatccctat cactacgaaa ttgtcattgg aactatgatt
 751  gttgggcaga gggatcatga caatcgagat atgccgccgc cacatcaacg
 801  ctaccacact ccaggtcggc aggatccagt tgacgatatg agtagattta
 851  taccaccagc ttccattcgt ccgcctccga tgaacatgca cacaaggcct
 901  cagcctatgc ctcaacaatt gccttcagtt ggcgcaacgt ttgcccatcc
 951  tctcccacat caggcgccac ataacccagg ggtttcacat ccgtactcca
1001  ttgctccaca gacccattac ccgttgaaca tgaacccaat tccgcaaatg
1051  ccgcaaatgc cacaaatgcc accacctctc catcagggat atggaatgaa
1101  tgggccgagt tgctcttcag aaaacaacaa tccattccac caaaatcacc
1151  attataatga tattagccat ccaaatcact attcctacga ctgtggtccg
1201  aacttgtacg ggtttccaac tccttatccg gattttcacc atcctttcaa
1251  tcagcaacca caccagccgc cacaactatc acaaaaccat acgtcccaac
1301  aaggcagtca tcaaccaggg caccaaggtc aggtaccgaa tgatccacca
1351  atttcaagac cagtgttaca accatcaaca gtcaccttgg acgtgttccg
1401  tcggtactgt agacagacat ttggaaatcg atttttgaa ggagaaagtg
1451  aacaatccgg cgcaataatt cggtctagta acaaattcat tgaagaattt
1501  gattcgccga tttgtggtgt gacagttgtt cgaccgcgga tgacagacgg
1551  tgaggttttg gagaacatca tgccggaaga tgcaccatat catgacattt
1601  gcaagttcat tttgaggctc acatcagaaa gtgtaacttt ctcaggagag
1651  gggccagaag ttagtgattt gaacgaaaaa tggggaacaa ttgtgtacta
1701  tgagaaaaat ttgcaaattg gcgagaaaaa atgttcgaga ggaaatttcc
1751  acgtggatgg cggattcatt tgctctgaga atcgttacag tctcggactt
1801  gagccaaatc caattagaga accagtggcg tttaaagttc gtaaagcaat
1851  agtggatgga attcgctttt cctacaaaaa agacgggagt gtttggcttc
1901  aaaaccgcat gaagtacccg gtatttgtca cttctgggta tctcgacgag
1951  caatcaggag gcctaaagaa ggataaagtg cacaaagttt acggatgtgc
2001  gtctatcaaa acgtttggct tcaacgtttc caaacaaatc atcagagacg
2051  cgcttctttc caagcaaatg gcaacaatgt acttgcaagg aaaattgact
```

Fig. 11A (sheet 1 of 2)

```
2101  ccgatgaatt atatctacga gaagaagact caggaagagc tgcgaaggga
2151  agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct
2201  cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat
2251  gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat
2301  ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg
2351  aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact
2401  tttttcactc accctactag atactgattt agtcttattc caaatcatcc
2451  aacgatatca aacttttcc tttgaacttt gcatactatg ttatcacaag
2501  ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa
2551  gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac
2601  aatgtatccc atacctcaat ctttaatagt catcagtcac tggtcccgca
2651  ccaatttttt cgattcgcat atgtcatata ttgcaccgtg gccctttta
2701  ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa
2751  ccaccatttt gagtaataaa tgtatttttt gtgg
```

Fig. 11A (sheet 2 of 2)

```
   1  gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
  51  ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gttcccgacg agcacacacc gatgatgtca ccagtgaata
 301  caactacaaa gattctacaa cggagtggta ttaaaatgga aatcccgcca
 351  tatttggatc cagacagtca ggatgatgac ccggaagatg gtgtcaacta
 401  cccggatcca gatttatttg acacaaaaaa cacaaatatg accgagtacg
 451  atttggatgt gttgaagctt ggaaaaccag cagtagatga agcacggaaa
 501  aagatcgaag ttcccgacgc tagtgcgccg ccaaacaaaa ttgtagaata
 551  tttgatgtat tatagaacgt taaaagaaag tgaactcata caactgaatg
 601  cgtatcggac aaaacgaaat cgattatcgt tgaacttggt caaaaacaat
 651  attgatcgag agttcgacca aaaagcttgc gagtccctgg tgaaaaaatt
 701  gaaggataag aagaatgatc tccagaacct gattgatgtg gttctttcaa
 751  aaggtacaaa atataccggt tgcattacaa ttccaaggac acttgatggc
 801  cggttacagg tccacggaag aaaaggtttc cctcacgtag tctatggcaa
 851  actgtggagg tttaatgaaa tgacaaaaaa cgaaacgcgt catgtggacc
 901  actgcaagca cgcatttgaa atgaaaagtg acatggtatg cgtgaatccc
 951  tatcactacg aaattgtcat tggaactatg attgttgggc agagggatca
1001  tgacaatcga gatatgccgc cgccacatca acgctaccac actccaggtc
1051  ggcaggatcc agttgacgat atgagtagat ttataccacc agcttccatt
1101  cgtccgcctc cgatgaacat gcacacaagg cctcagccta tgcctcaaca
1151  attgccttca gttggcgcaa cgtttgccca tcctctccca catcaggcgc
1201  cacataaccc aggggtttca catccgtact ccattgctcc acagacccat
1251  tacccgttga acatgaaccc aattccgcaa atgccgcaaa tgccacaaat
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1401  catccaaatc actattccta cgactgtggt ccgaacttgt acgggtttcc
1451  aactccttat ccggattttc accatccttt caatcagcaa ccacaccagc
1501  cgccacaact atcacaaaac catacgtccc aacaaggcag tcatcaacca
1551  gggcaccaag gtcaggtacc gaatgatcca ccaatttcaa gaccagtgtt
1601  acaaccatca acagtcacct tggacgtgtt ccgtcggtac tgtagacaga
1651  catttggaaa tcgatttttt gaaggagaaa gtgaacaatc cggcgcaata
1701  attcggtcta gtaacaaatt cattgaagaa tttgattcgc cgatttgtgg
1751  tgtgacagtt gttcgaccgc ggatgacaga cggtgaggtt ttggagaaca
1801  tcatgccgga agatgcacca tatcatgaca tttgcaagtt cattttgagg
1851  ctcacatcag aaagtgtaac tttctcagga gaggggccag aagttagtga
1901  tttgaacgaa aaatggggaa caattgtgta ctatgagaaa aatttgcaaa
1951  ttggcgagaa aaaatgttcg agaggaaatt tccacgtgga tggcggattc
2001  atttgctctg agaatcgtta cagtctcgga cttgagccaa atccaattag
2051  agaaccagtg gcgtttaaag ttcgtaaagc aatagtggat ggaattcgct
```

Fig. 11B (sheet 1 of 2)

```
2101  tttcctacaa aaaagacggg agtgtttggc ttcaaaaccg catgaagtac
2151  ccggtatttg tcacttctgg gtatctcgac gagcaatcag gaggcctaaa
2201  gaaggataaa gtgcacaaag tttacggatg tgcgtctatc aaaacgtttg
2251  gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa
2301  atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta
2351  cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg
2401  attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt
2451  ggagaagcat acccagaacg cccgtcaatt catgattgtc cagtttggat
2501  tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt
2551  acataaccaa ctgcttcgag ccgctaggaa tggaagattt tgcaaaattg
2601  ggaatcaacg tcagtgatga ctaaatgata actttttca ctcaccctac
2651  tagatactga tttagtctta ttccaaatca tccaacgata tcaaactttt
2701  tcctttgaac tttgcatact atgttatcac aagttccaag cagtttcaat
2751  acaaacatag gatatgttaa caacttttga taagaatcaa gttaccaact
2801  gttcattgtg agctttgagc tgtatagaag gacaatgtat cccatacctc
2851  aatctttaat agtcatcagt cactggtccc gcaccaattt tttcgattcg
2901  catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaatata
2951  ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat
3001  aaatgtattt tttgtgg
```

Fig. 11B (sheet 2 of 2)

```
   1  gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
  51  ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gaatttaaac caataatcac attggacacg aaaccacctc
 301  gtgatgccaa caagtcattg gcattcaatg gcgggttgaa gctaatcact
 351  ccgaaaactg aagttcccga cgagcacaca ccgatgatgt caccagtgaa
 401  tacaactaca aagattctac aacggagtgg tattaaaatg gaaatcccgc
 451  catatttgga tccagacagt caggatgatg acccggaaga tggtgtcaac
 501  tacccggatc cagatttatt tgacacaaaa aacacaaata tgaccgagta
 551  cgatttggat gtgttgaagc ttggaaaacc agcagtagat gaagcacgga
 601  aaaagatcga agttcccgac gctagtgcgc cgccaaacaa aattgtagaa
 651  tatttgatgt attatagaac gttaaaagaa agtgaactca tacaactgaa
 701  tgcgtatcgg acaaaacgaa atcgattatc gttgaacttg gtcaaaaaca
 751  atattgatcg agagttcgac caaaaagctt gcgagtccct ggtgaaaaaa
 801  ttgaaggata agaagaatga tctccagaac ctgattgatg tggttctttc
 851  aaaaggtaca aaatataccg gttgcattac aattccaagg acacttgatg
 901  gccggttaca ggtccacgga agaaaaggtt tccctcacgt agtctatggc
 951  aaactgtgga ggtttaatga aatgacaaaa aacgaaacgc gtcatgtgga
1001  ccactgcaag cacgcatttg aaatgaaaag tgacatggta tgcgtgaatc
1051  cctatcacta cgaaattgtc attggaacta tgattgttgg gcagagggat
1101  catgacaatc gagatatgcc gccgccacat caacgctacc acactccagg
1151  tcggcaggat ccagttgacg atatgagtag atttatacca ccagcttcca
1201  ttcgtccgcc tccgatgaac atgcacacaa ggcctcagcc tatgcctcaa
1251  caattgcctt cagttggcgc aacgtttgcc catcctctcc cacatcaggc
1301  gccacataac ccaggggttt cacatccgta ctccattgct ccacagaccc
1351  attacccgtt gaacatgaac ccaattccgc aaatgccgca aatgccacaa
1401  atgccaccac ctctccatca gggatatgga atgaatgggc cgagttgctc
1451  ttcagaaaac aacaatccat tccaccaaaa tcaccattat aatgatatta
1501  gccatccaaa tcactattcc tacgactgtg gtccgaactt gtacgggttt
1551  ccaactcctt atccggattt tcaccatcct ttcaatcagc aaccacacca
1601  gccgccacaa ctatcacaaa accatacgtc ccaacaaggc agtcatcaac
1651  cagggcacca aggtcaggta ccgaatgatc caccaatttc aagaccagtg
1701  ttacaaccat caacagtcac cttggacgtg ttccgtcggt actgtagaca
1751  gacatttgga aatcgatttt ttgaaggaga aagtgaacaa tccggcgcaa
1801  taattcggtc tagtaacaaa ttcattgaag aatttgattc gccgatttgt
1851  ggtgtgacag ttgttcgacc gcggatgaca gacggtgagg ttttggagaa
1901  catcatgccg gaagatgcac catatcatga catttgcaag ttcattttga
1951  ggctcacatc agaaagtgta actttctcag gagaggggcc agaagttagt
2001  gatttgaacg aaaaatgggg aacaattgtg tactatgaga aaaatttgca
2051  aattggcgag aaaaaatgtt cgagaggaaa tttccacgtg gatggcggat
```

Fig. 11C (sheet 1 of 2)

```
2101  tcatttgctc tgagaatcgt tacagtctcg gacttgagcc aaatccaatt
2151  agagaaccag tggcgtttaa agttcgtaaa gcaatagtgg atggaattcg
2201  cttttcctac aaaaaagacg ggagtgtttg gcttcaaaac cgcatgaagt
2251  acccggtatt tgtcacttct gggtatctcg acgagcaatc aggaggccta
2301  aagaaggata aagtgcacaa agtttacgga tgtgcgtcta tcaaaacgtt
2351  tggcttcaac gtttccaaac aaatcatcag agacgcgctt ctttccaagc
2401  aaatggcaac aatgtacttg caaggaaaat tgactccgat gaattatatc
2451  tacgagaaga agactcagga agagctgcga agggaagcaa cacgcaccac
2501  tgattcattg gccaagtact gttgtgtccg tgtctcgttc tgcaaaggat
2551  ttggagaagc atacccagaa cgcccgtcaa ttcatgattg tccagtttgg
2601  attgagttga aaatcaacat tgcctacgat ttcatggatt caatctgcca
2651  gtacataacc aactgcttcg agccgctagg aatggaagat tttgcaaaat
2701  tgggaatcaa cgtcagtgat gactaaatga taacttttt cactcaccct
2751  actagatact gatttagtct tattccaaat catccaacga tatcaaactt
2801  tttcctttga actttgcata ctatgttatc acaagttcca agcagtttca
2851  atacaaacat aggatatgtt aacaactttt gataagaatc aagttaccaa
2901  ctgttcattg tgagctttga gctgtataga aggacaatgt atcccatacc
2951  tcaatcttta atagtcatca gtcactggtc ccgcaccaat tttttcgatt
3001  cgcatatgtc atatattgca ccgtggccct ttttattgta acttttaata
3051  tattttcttc ccaacttgtg aatatgattg atgaaccacc attttgagta
3101  ataaatgtat tttttgtgg
```

Fig. 11C (sheet 2 of 2)

```
  1  MKLIATSLLV PDEHTPMMSP VNTTTKILQR SGIKMEIPPY LDPDSQDDDP
 51  EDGVNYPDPD LFDTKNTNMT EYDLDVLKLG KPAVDEARKK IEVPDASAPP
101  NKIVEYLMYY RTLKESELIQ LNAYRTKRNR LSLNLVKNNI DREFDQKACE
151  SLVKKLKDKK NDLQNLIDVV LSKGTKYTGC ITIPRTLDGR LQVHGRKGFP
201  HVVYGKLWRF NEMTKNETRH VDHCKHAFEM KSDMVCVNPY HYEIVIGTMI
251  VGQRDHDNRD MPPPHQRYHT PGRQDPVDDM SRFIPPASIR PPPMNMHTRP
301  QPMPQQLPSV GATFAHPLPH QAPHNPGVSH PYSIAPQTHY PLNMNPIPQM
351  PQMPQMPPPL HQGYGMNGPS CSSENNNPFH QNHHYNDISH PNHYSYDCGP
401  NLYGFPTPYP DFHHPFNQQP HQPPQLSQNH TSQQGSHQPG HQGQVPNDPP
451  ISRPVLQPST VTLDVFRRYC RQTFGNRFFE GESEQSGAII RSSNKFIEEF
501  DSPICGVTVV RPRMTDGEVL ENIMPEDAPY HDICKFILRL TSESVTFSGE
551  GPEVSDLNEK WGTIVYYEKN LQIGEKKCSR GNFHVDGGFI CSENRYSLGL
601  EPNPIREPVA FKVRKAIVDG IRFSYKKDGS VWLQNRMKYP VFVTSGYLDE
651  QSGGLKKDKV HKVYGCASIK TFGFNVSKQI IRDALLSKQM ATMYLQGKLT
701  PMNYIYEKKT QEELRREATR TTDSLAKYCC VRVSFCKGFG EAYPERPSIH
751  DCPVWIELKI NIAYDFMDSI CQYITNCFEP LGMEDFAKLG INVSDD
```

Fig. 12A

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NVPDEHTPMM SPVNTTTKIL QRSGIKMEIP
101 PYLDPDSQDD DPEDGVNYPD PDLFDTKNTN MTEYDLDVLK LGKPAVDEAR
151 KKIEVPDASA PPNKIVEYLM YYRTLKESEL IQLNAYRTKR NRLSLNLVKN
201 NIDREFDQKA CESLVKKLKD KKNDLQNLID VVLSKGTKYT GCITIPRTLD
251 GRLQVHGRKG FPHVVYGKLW RFNEMTKNET RHVDHCKHAF EMKSDMVCVN
301 PYHYEIVIGT MIVGQRDHDN RDMPPPHQRY HTPGRQDPVD DMSRFIPPAS
351 IRPPPMNMHT RPQPMPQQLP SVGATFAHPL PHQAPHNPGV SHPYSIAPQT
401 HYPLNMNPIP QMPQMPQMPP PLHQGYGMNG PSCSSENNNP FHQNHHYNDI
451 SHPNHYSYDC GPNLYGFPTP YPDFHHPFNQ QPHQPPQLSQ NHTSQQGSHQ
501 PGHQGQVPND PPISRPVLQP STVTLDVFRR YCRQTFGNRF FEGESEQSGA
551 IIRSSNKFIE EFDSPICGVT VVRPRMTDGE VLENIMPEDA PYHDICKFIL
601 RLTSESVTFS GEGPEVSDLN EKWGTIVYYE KNLQIGEKKC SRGNFHVDGG
651 FICSENRYSL GLEPNPIREP VAFKVRKAIV DGIRFSYKKD GSVWLQNRMK
701 YPVFVTSGYL DEQSGGLKKD KVHKVYGCAS IKTFGFNVSK QIIRDALLSK
751 QMATMYLQGK LTPMNYIYEK KTQEELRREA TRTTDSLAKY CCVRVSFCKG
801 FGEAYPERPS IHDCPVWIEL KINIAYDFMD SICQYITNCF EPLGMEDFAK
851 LGINVSDD
```

Fig. 12B

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NEFKPIITLD TKPPRDANKS LAFNGGLKLI
101 TPKTEVPDEH TPMMSPVNTT TKILQRSGIK MEIPPYLDPD SQDDDPEDGV
151 NYPDPDLFDT KNTNMTEYDL DVLKLGKPAV DEARKKIEVP DASAPPNKIV
201 EYLMYYRTLK ESELIQLNAY RTKRNRLSLN LVKNNIDREF DQKACESLVK
251 KLKDKKNDLQ NLIDVVLSKG TKYTGCITIP RTLDGRLQVH GRKGFPHVVY
301 GKLWRFNEMT KNETRHVDHC KHAFEMKSDM VCVNPYHYEI VIGTMIVGQR
351 DHDNRDMPPP HQRYHTPGRQ DPVDDMSRFI PPASIRPPPM NMHTRPQPMP
401 QQLPSVGATF AHPLPHQAPH NPGVSHPYSI APQTHYPLNM NPIPQMPQMP
451 QMPPPLHQGY GMNGPSCSSE NNNPFHQNHH YNDISHPNHY SYDCGPNLYG
501 FPTPYPDFHH PFNQQPHQPP QLSQNHTSQQ GSHQPGHQGQ VPNDPPISRP
551 VLQPSTVTLD VFRRYCRQTF GNRFFEGESE QSGAIIRSSN KFIEEFDSPI
601 CGVTVVRPRM TDGEVLENIM PEDAPYHDIC KFILRLTSES VTFSGEGPEV
651 SDLNEKWGTI VYYEKNLQIG EKKCSRGNFH VDGGFICSEN RYSLGLEPNP
701 IREPVAFKVR KAIVDGIRFS YKKDGSVWLQ NRMKYPVFVT SGYLDEQSGG
751 LKKDKVHKVY GCASIKTFGF NVSKQIIRDA LLSKQMATMY LQGKLTPMNY
801 IYEKKTQEEL RREATRTTDS LAKYCCVRVS FCKGFGEAYP ERPSIHDCPV
851 WIELKINIAY DFMDSICQYI TNCFEPLGME DFAKLGINVS DD
```

Fig. 12C

tgatctttcaagccgaagcaatcaagacctcaaagccaatcaactctactcacttttcttcagaaccttaacttttttgtg
tcactttccccaaaaaccgttcaagctgctgccttcactctcatcccctcctcttactccttctttctcgtccgctacta
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Fig. 13A

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Fig. 13B

MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTPDDVMMNDDMEPIPRDR
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TTAIMASPEKRLTLAQVYEWMVQNVPYFRDKGDSNSSAGWKNSIRHNLSLH
SRFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
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Fig. 14A

MQQYIYQESSATIPHHHLNQHNNPYHPMHPHHQLPHMQQLPQPLLNLNMTT
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FRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDRT
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Fig. 14B

```
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 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa
 181 ggtgtcgcag atatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg
 241 tggtttcttg caaatgtgcg aacatcgcta gaaatcaagc tatcagattt caaacatcaa
 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat
 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc
 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga
 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctcactggat
 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt
 601 acgaagaaaa cgtgcttgac acgtggactt gagggtacca gtcactacgc gttccccgaa
 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaatcaaa agtcaaggct
 721 gccaagctga gttatcagat gttttggaga aaacgtaaag cggaaatcaa tggagtttgc
 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt
 841 cacacgtttc tctacgaaat gcgaaaattg gatgtatacg ataccgatga tcctgcagat
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2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt
2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca
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Fig. 15 (sheet 1 of 2)

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2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg
2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc
2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag
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```

Fig. 15 (sheet 2 of 2)

```
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  61 GVADIITMCP FGEVISVVFP WFLANVRTSL EIKLSDFKHQ LFELIAPMKW GTYSVKPQDY
 121 VFRQLNNFGE IEVIFNDDQP LSKLELHGTF PMLFLYQPDG INRDKELMSD ISHCLGYSLD
 181 KLEESLDEEL RQFRASLWAR TKKTCLTRGL EGTSHYAFPE EQYLCVGESC PKDLESKVKA
 241 AKLSYQMFWR KRKAEINGVC EKMMKIQIEF NPNETPKSLL HTFLYEMRKL DVYDTDDPAD
 301 EGWFLQLAGR TTFVTNPDVK LTSYDGVRSE LESYRCPGFV VRRQSLVLKD YCRPKPLYEP
 361 HYVRAHERKL ALDVLSVSID STPKQSKNSD MVMTDFRPTA SLKQVSLWDL DANLMIRPVN
 421 ISGFDFPADV DMYVRIEFSV YVGTLTLASK STTKVNAQFA KWNKEMYTFD LYMKDMPPSA
 481 VLSIRVLYGK VKLKSEEFEV GWVNMSLTDW RDELRQGQFL FHLWAPEPTA NRSRIGENGA
 541 RIGTNAAVTI EISSYGGRVR MPSQGQYTYL VKHRSTWTET LNIMGDDYES CIRDPGYKKL
 601 QMLVKKHESG IVLEEDEQRH VWMWRRYIQK QEPDLLIVLS ELAFVWTDRE NFSELYVMLE
 661 KWKPPSVAAA LTLLGKRCTD RVIRKFAVEK LNEQLSPVTF HLFILPLIQA LKYEPRAQSE
 721 VGMMLLTRAL CDYRIGHRLF WLLRAEIARL RDCDLKSEEY RRISLLMEAY LRGNEEHIKI
 781 ITRQVDMVDE LTRISTLVKG MPKDVATMKL RDELRSISHK MENMDSPLDP VYKLGEMIID
 841 KAIVLGSAKR PLMLHWKNKN PKSDLHLPFC AMIFKNGDDL RQDMLVLQVL EVMDNIWKAA
 901 NIDCCLNPYA VLPMGEMIGI IEVVPNCKTI FEIQVGTGFM NTAVRSIDPS FMNKWIRKQC
 961 GIEDEKKKSK KDSTKNPIEK KIDNTQAMKK YFESVDRFLY SCVGYSVATY IMGIKDRHSD
1021 NLMLTEDGKY VHIDFGHILG HGKTKLGIQR DRQPFILTEH FMTVIRSGKS VDGNSHELQK
1081 FKTLCVEAYE VMWNNRDLFV SLFTLMLGME LPELSTKADL DHLKKTLFCN GESKEEARKF
1141 FAGIYEEAFN GSWSTKTNWL FHAVKHY
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Fig. 16

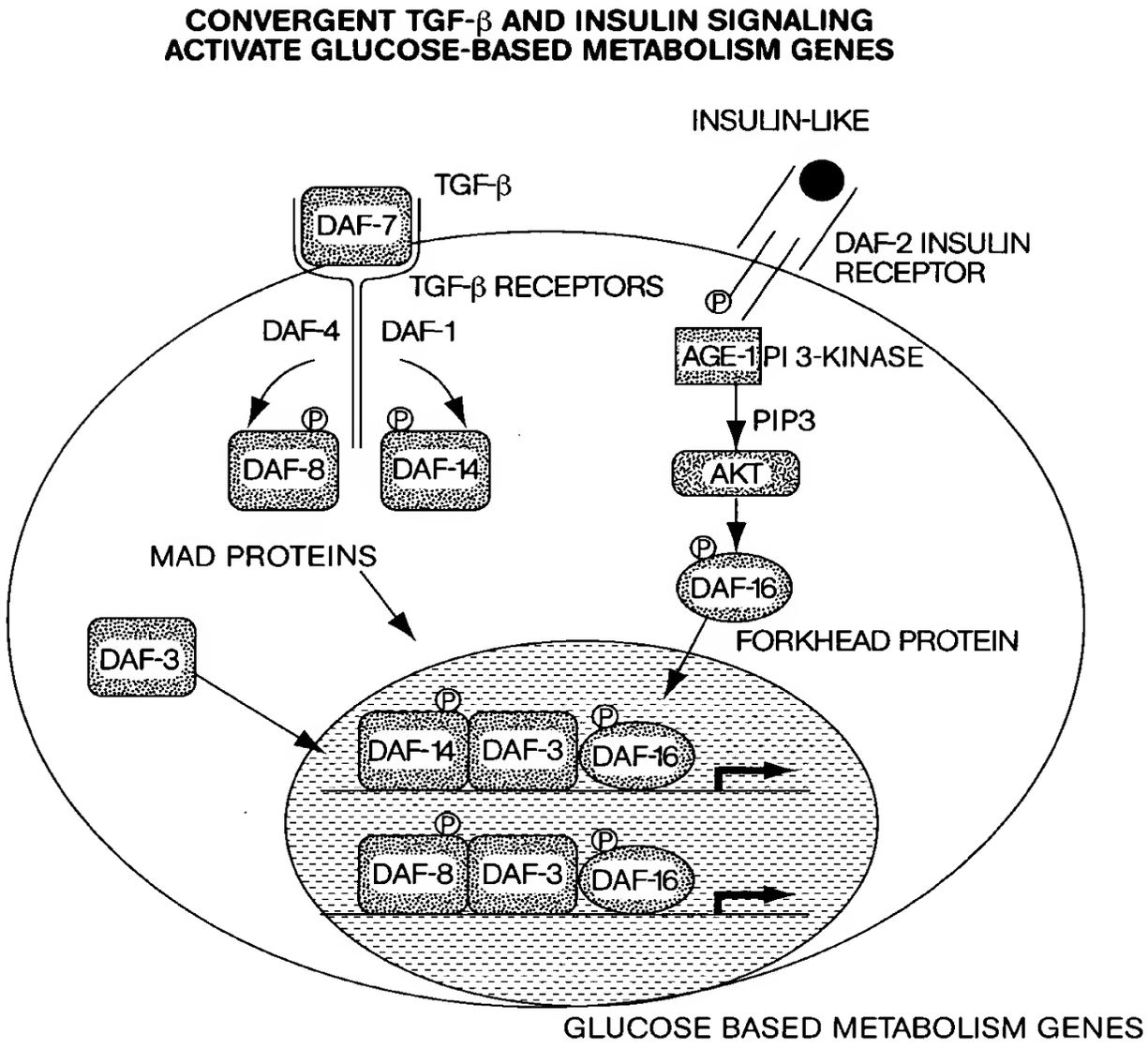

CONVERGENT TGF-β AND INSULIN SIGNALING
ACTIVATE GLUCOSE-BASED METABOLISM GENES
INSULIN-LIKE
TGF-β
DAF-7
DAF-2 INSULIN
RECEPTOR
TGF-β RECEPTORS
DAF-4
DAF-1
AGE-1 PI 3-KINASE
PIP3
DAF-8
DAF-14
AKT
MAD PROTEINS
DAF-16
FORKHEAD PROTEIN
DAF-3
DAF-14
DAF-3
DAF-16
DAF-8
DAF-3
DAF-16
GLUCOSE BASED METABOLISM GENES

Fig. 17

IN PHEROMONE, NO TGFβ OR INSULIN-LIKE SIGNALS CAUSES REPRESSION OF ANABOLIC GENES

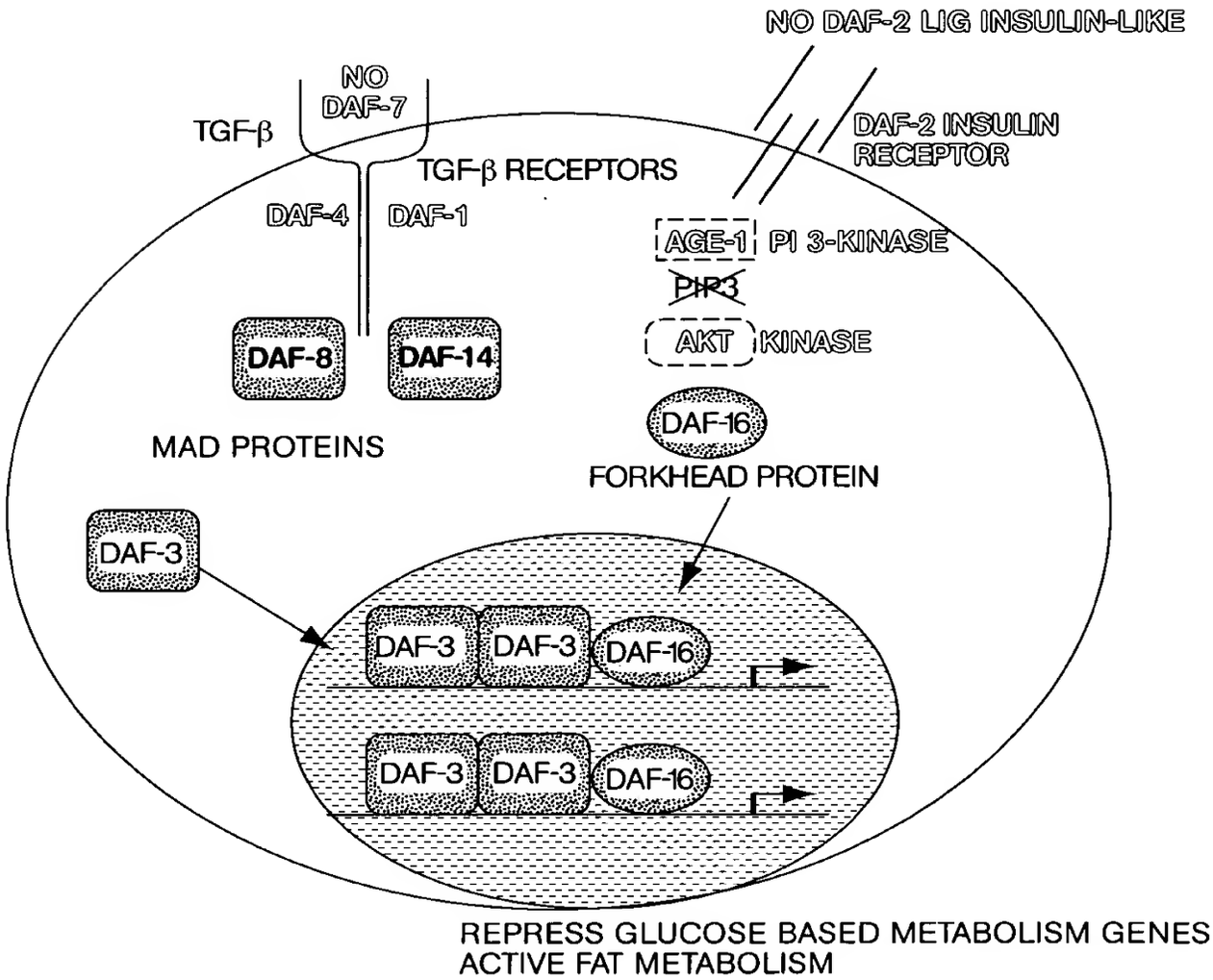
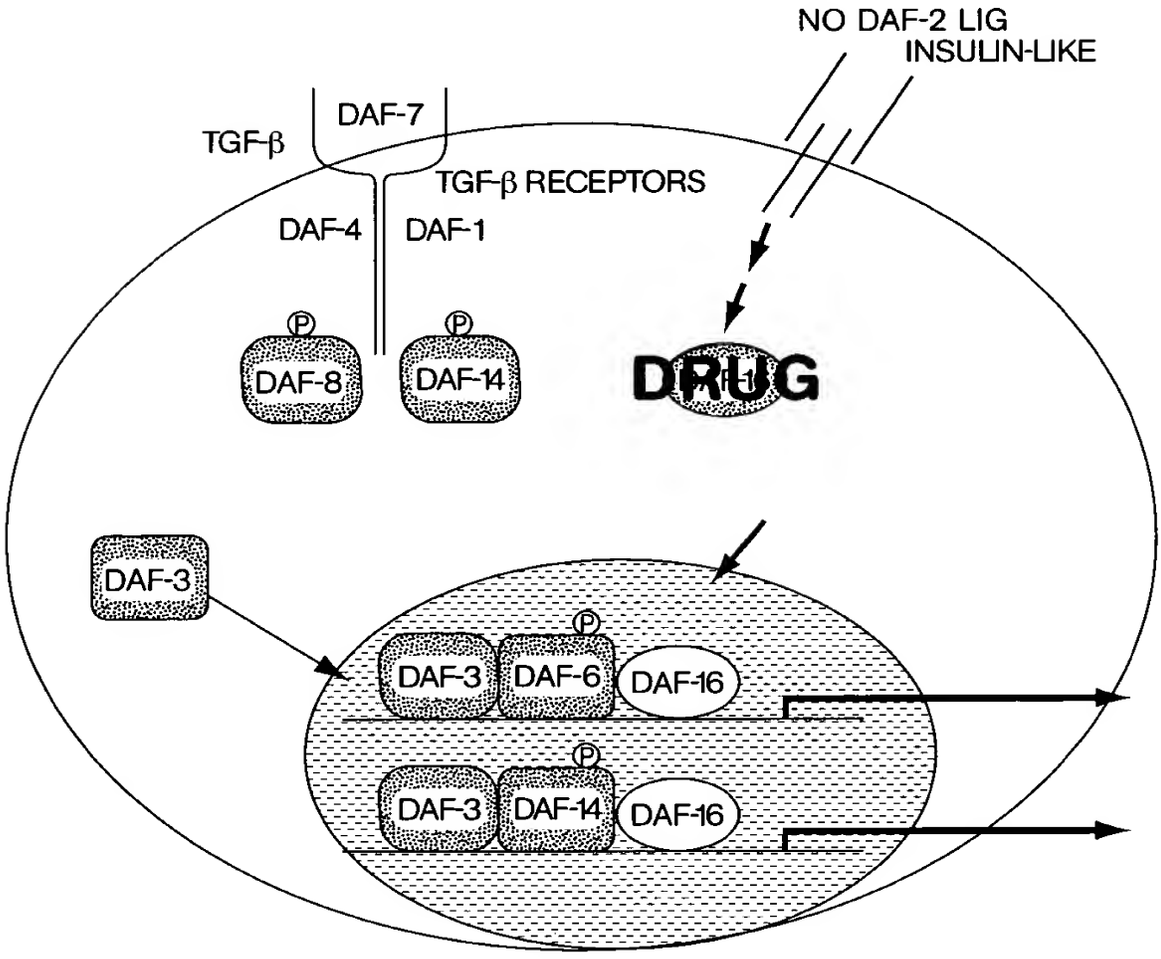


Fig. 18

**DRUGS THAT INHIBIT DAF-16 OR DAF-3
(OR PROTEINS IN THE PATHWAY)
CAN BE DISCOVERED USING REPORTER GENES
BEARING THEIR COGNATE BINDING SITES**



DRUG CAUSES A DECREASE IN DAF-16 ACTIVITY, ACTIVATING
THE REPORTER GENE LIKE A DAF-16 MUTANT.
THIS BYPASSES THE NEED FOR INSULIN

Fig. 19

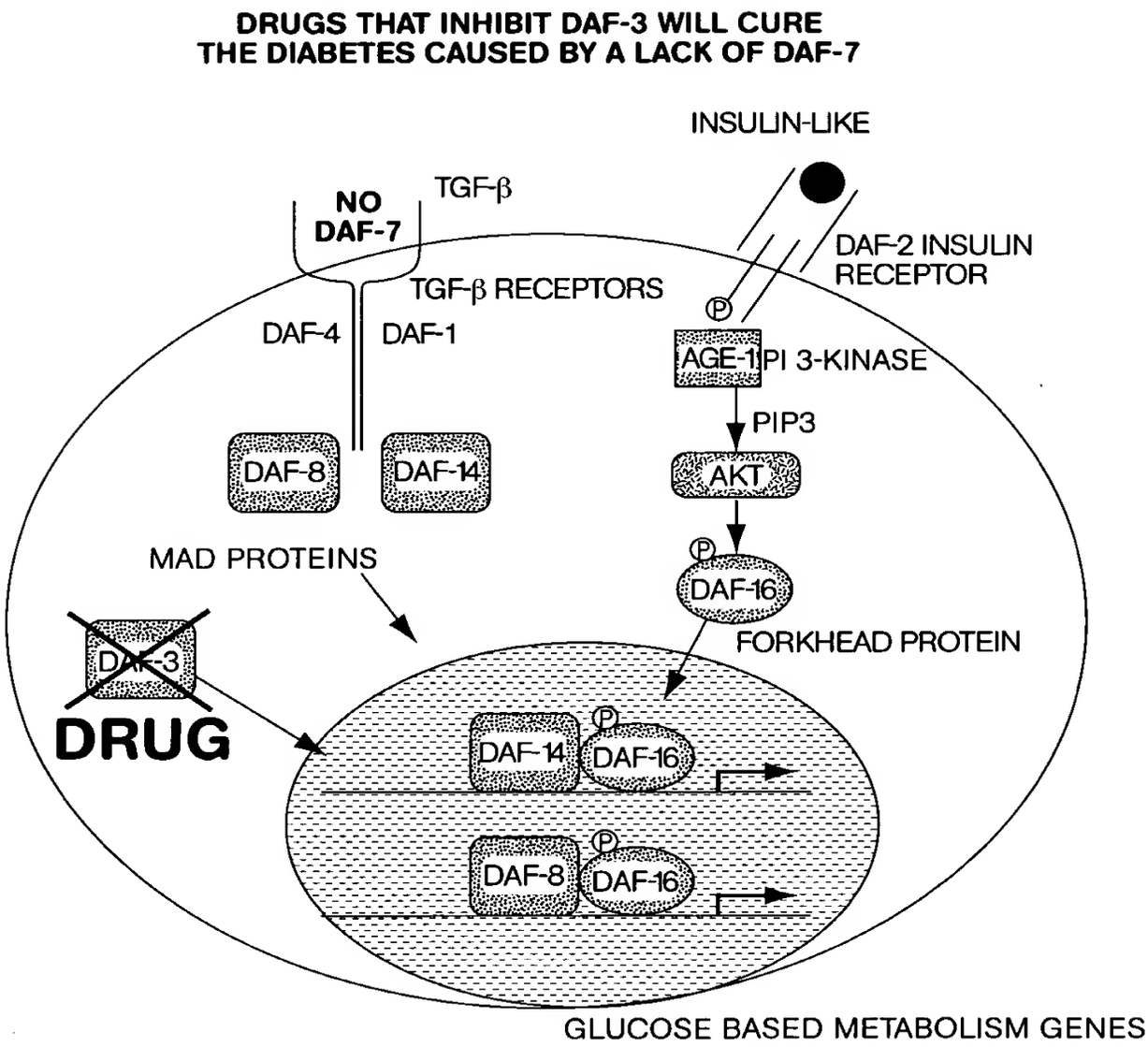

DRUGS THAT INHIBIT DAF-3 WILL CURE
THE DIABETES CAUSED BY A LACK OF DAF-7
INSULIN-LIKE
TGF-β
NO
DAF-7
DAF-2 INSULIN
RECEPTOR
TGF-β RECEPTORS
DAF-4
DAF-1
AGE-1
PI 3-KINASE
PIP3
DAF-8
DAF-14
AKT
MAD PROTEINS
DAF-16
FORKHEAD PROTEIN
DAF-3
DRUG
DAF-14
DAF-16
DAF-8
DAF-16
GLUCOSE BASED METABOLISM GENES

Fig. 20

Fig. 21A (sheet 1 of 2)

```
DAF-16a1   511 ------------------------------------------------------------------------
DAF-16b    531 ------------------------------------------------------------------------
FKHR       511 ASHNKMMNPSSH.THPGHAQQTSAVNGRPLPHTVSTMPHTSGMNRLTQVKTPVQVPLPHPMQMSALGGYSSVSSCNGYGR
FKHRL1     523 PNQGSLVN.QNL.LHHQHQTQGALGGSRALSNSVSNM.GLSESSSLGSAKHQQQSPVSQSMQ.TLSDSLSGSSLYSTSAN
AFX        464 QDLDLDMYMENLECDMDNIISDLMDEGEGLDFNFEPDP------------------------------------------

DAF-16a1   511 ---------------------------------------------------------------
DAF-16b    531 ---------------------------------------------------------------
FKHR       590 MGLLHQEKLPSDLD.GMFIERLDCDMESILRNDLMDGDILDFNFDNVLPNQ........SFPHSVKTTTHSWVSG
FKHRL1     599 LPVMGHEKFPSDLDLDMFNGSLECDMESIIRSELMDADGLDFNFDSLISTQNVVGLNVGNFTGAKQASSQSWVPG
AFX        502 ---------------------------------------------------------------
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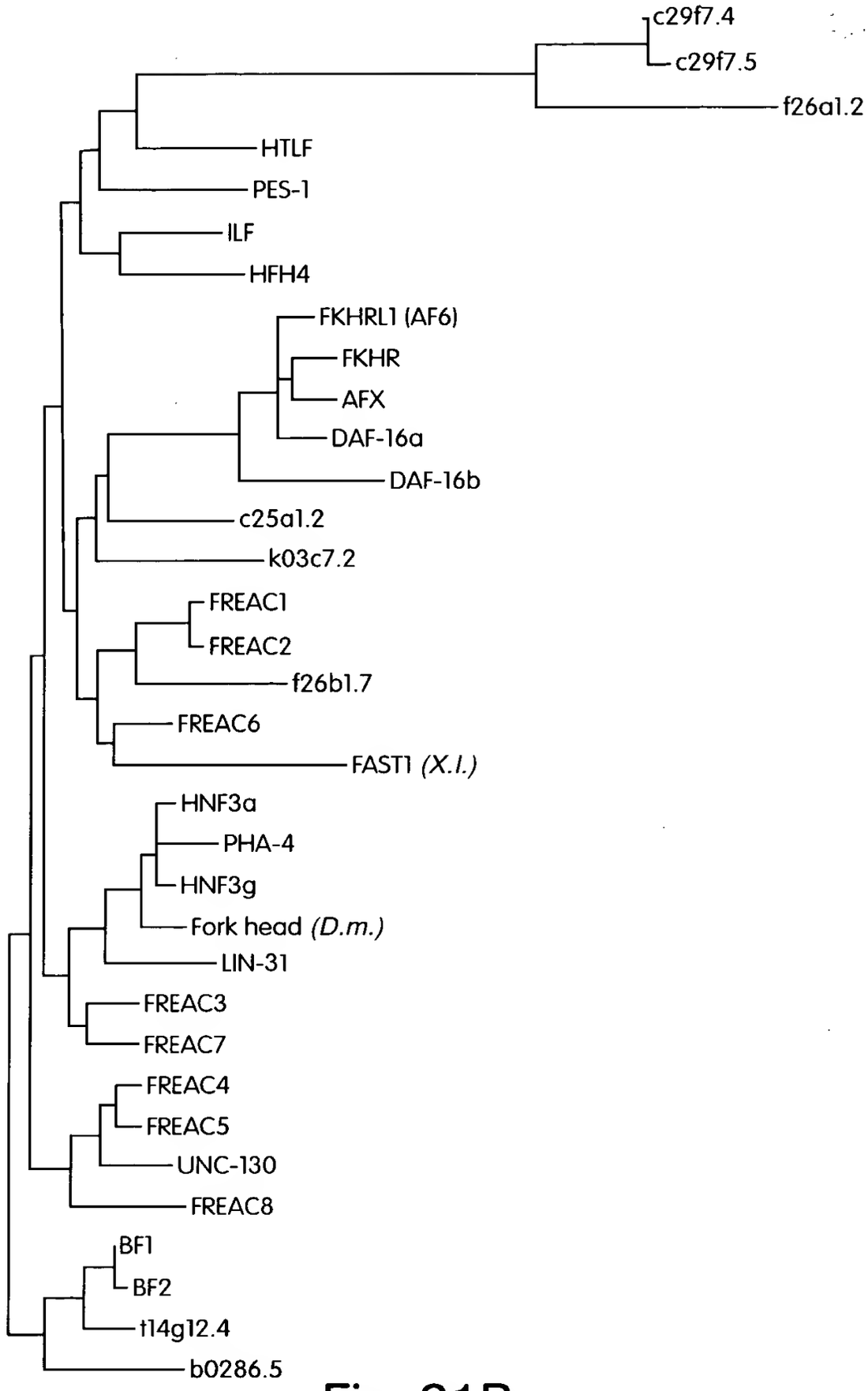
Fig. 21A (sheet 2 of 2)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c29f7.5
f26a1.2
HTLF
PES-1
ILF
HFH4
FKHRL1 (AF6)
FKHR
AFX
DAF-16a
DAF-16b
c25a1.2
k03c7.2
FREAC1
FREAC2
f26b1.7
FREAC6
FAST1 (X.l.)
HNF3a
PHA-4
HNF3g
Fork head (D.m.)
LIN-31
FREAC3
FREAC7
FREAC4
FREAC5
UNC-130
FREAC8
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BF2
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Fig. 21B

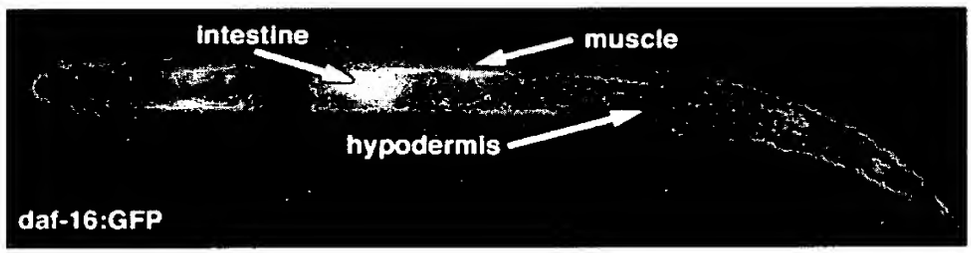
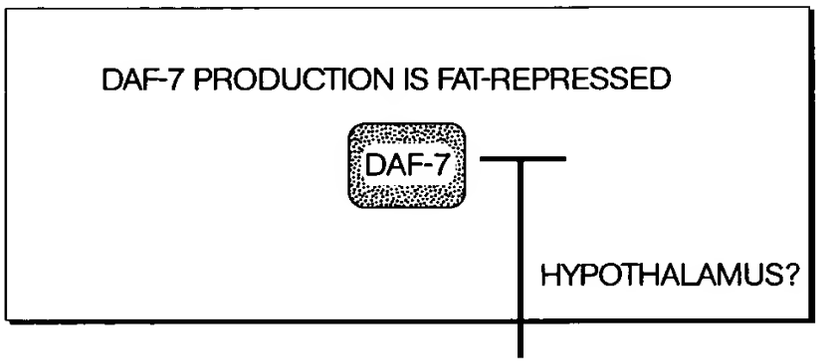


Fig. 22

INJECTION OF OF DAF-7 BYPASSES OBESITY-INDUCED DEFECTS IN INSULIN-REGULATION OF METABOLISM



FATTY ACIDS IN BLOOD REPRESS DAF-7 IN ANALOGY TO PHEROMONE REGULATION OF DAF-7 IN C. ELEGANS

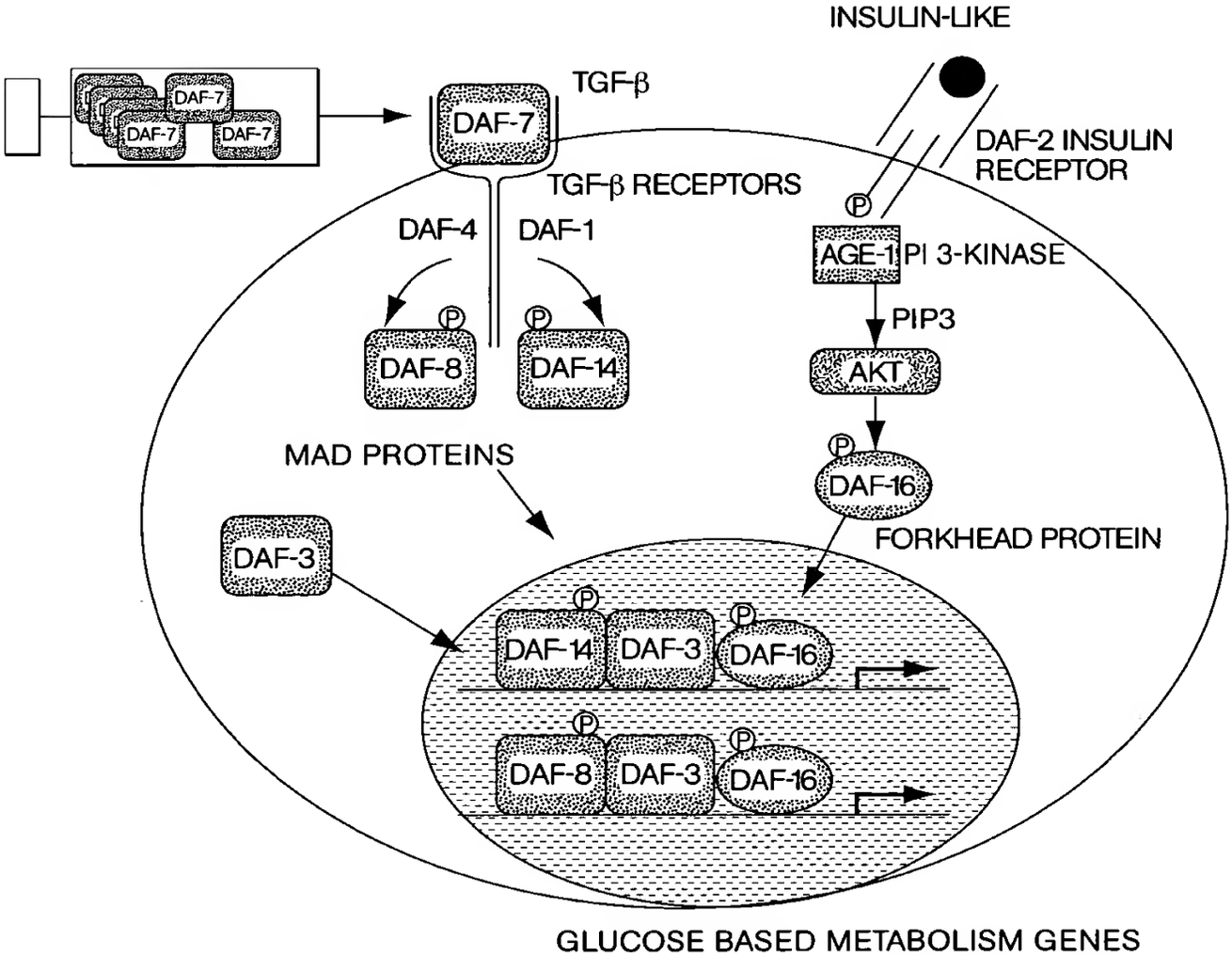


Fig. 23

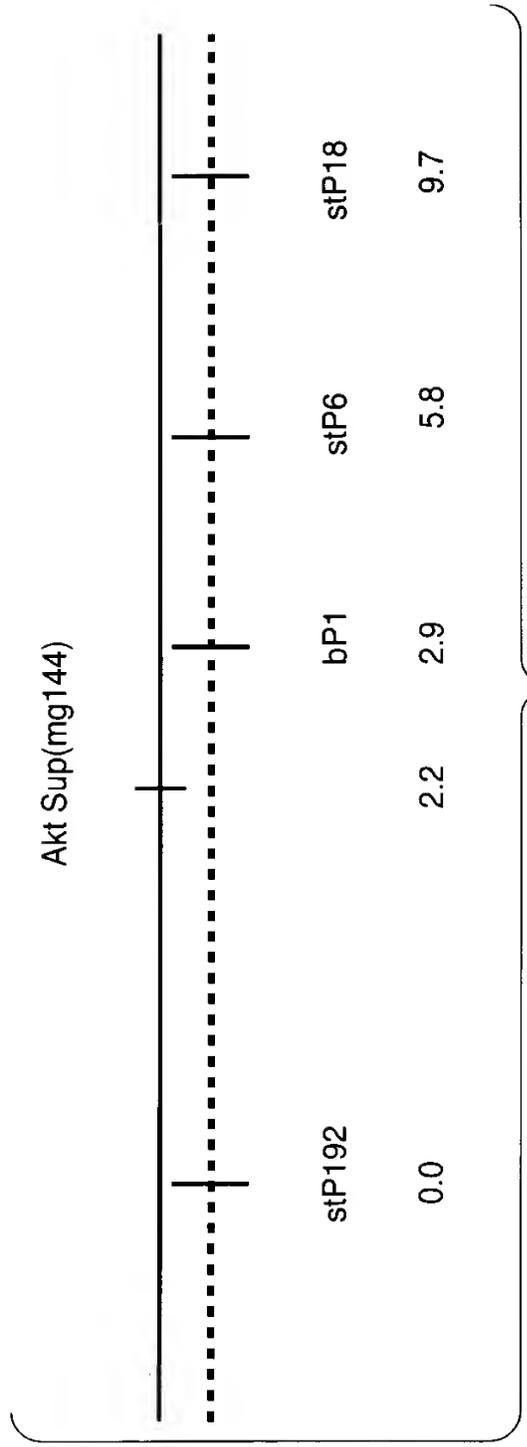


Fig. 24

Comparison of the human AKT protein sequence to the cosmid sequence C12D8, located in the genetic interval where sup(mg144) maps. Numbering in the AKT protein sequence by amino acid residues, and in the cosmid sequence by nucleotide position.

```
 Score = 450 (207.4 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 79/121 (65%), Positives = 97/121 (80%), Frame = +1

Query:    319 EVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILMEEIRFPRTLGPEAKS 378
              +VL+D+DYGR VDWWG+GVVMYEMMCGRLPFY++DH KLFELI+  ++RFP  L  EA++
Sbjct:  33685 QVLDDHDYGRCVDWWGVGVVMYEMMCGRLPFYSKDHNKLFELIMAGDLRFPSKLSQEART 33864

Query:    379 LLSGLLKKDPTQRLGGGSEDAKEIMQHRFFANIVWQDVYEKKLSPPFKPQVTSETDTRYFD 439
              LL+GLL KDPTQRLGGG EDA EI +  FF  + W+  Y K++ PP+KP V SETDT YFD
Sbjct:  33865 LLTGLLVKDPTQRLGGGPEDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFD 34047

 Score = 256 (118.0 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 48/66 (72%), Positives = 59/66 (89%), Frame = +1

Query:    146 TMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKILKKEVIVAKDEVAHTLTENRVLQNS 205
              TM +F++LK+LGKGTFGKVIL KEK T + YA+KILKK+VI+A++EVAHTLTENRVLQ
Sbjct:  32314 TMEDFDFLKVLGKGTFGKVILCKEKRTQKLYAIKILKKDVIIAREEVAHTLTENRVLQRC 32493

Query:    206 RHPFLT 211
              +HPFLT
Sbjct:  32494 KHPFLT 32511

 Score = 190 (87.6 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 36/45 (80%), Positives = 37/45 (82%), Frame = +2

Query:    276 KLENLMLDKDGHIKITDFGLCKEGIKDGATMKTFCGTPEYLAPEV 320
              KLENL+LDKDGHIKI DFGLCKE I  G    TFCGTPEYLAPEV
Sbjct:  33509 KLENLLLDKDGHIKIADFGLCKEEISFGDKTSTFCGTPEYLAPEV 33643

 Score = 188 (86.7 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 37/57 (64%), Positives = 42/57 (73%), Frame = +3

Query:    209 FLTALKYSFQTHDRLCFVMEYANGGELFFHLSRERVFSEDRARFYGAEIVSALDYLH 265
              +   LKYSFQ    LCFVM++ANGGELF H+ +   FSE RARFYGAEIV AL YLH
Sbjct:  32667 YFQELKYSFQEQHYLCFVMQFANGGELFTHVRKCGTFSEPRARFYGAEIVLALGYLH 32837

 Score = 166 (76.5 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 29/59 (49%), Positives = 42/59 (71%), Frame = +1

Query:     53 NNFSVAQCQLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREEWATAIQTVADGLK 111
              + F++   Q M  E+PRPN F++RCLQWTTVIERTF+ E+ E R+ W  AI++++   K
Sbjct:  31846 STFAIFYFQTMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESISKKYK 32022

 Score = 134 (61.8 bits), Expect = 5.2e-167, Sum P(8) = 5.2e-167
 Identities = 24/33 (72%), Positives = 30/33 (90%), Frame = +3

Query:    210 LTALKYSFQTHDRLCFVMEYANGGELFFHLSRE 242
              L  LKYSFQT+DRLCFVME+A GG+L++HL+RE
Sbjct:  33156 LQELKYSFQTNDRLCFVMEFAIGGDLYYHLNRE 33254
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Fig. 25

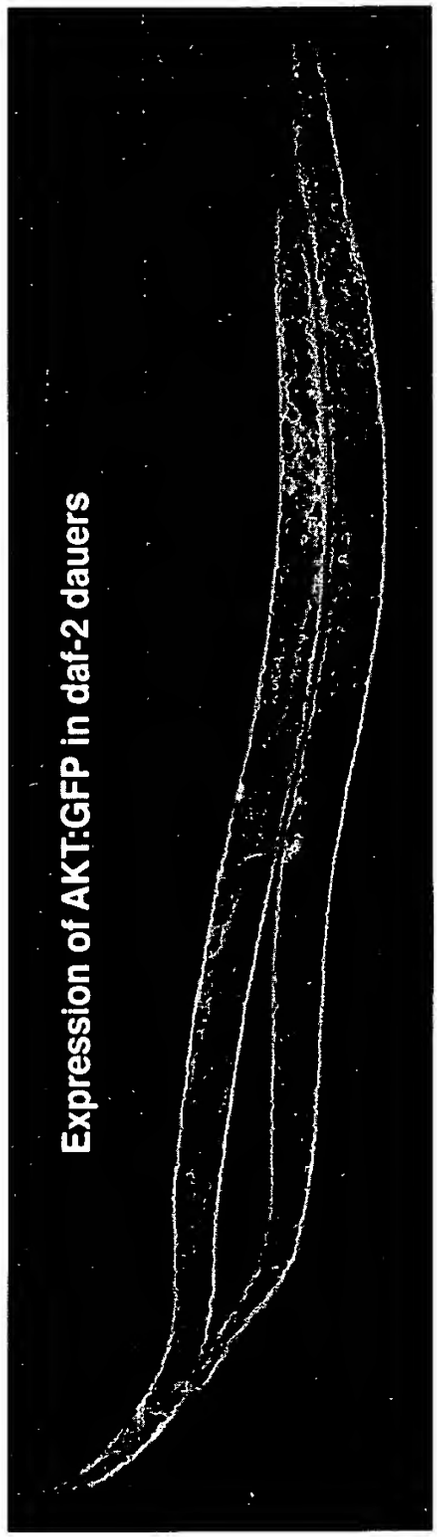


Fig. 26A

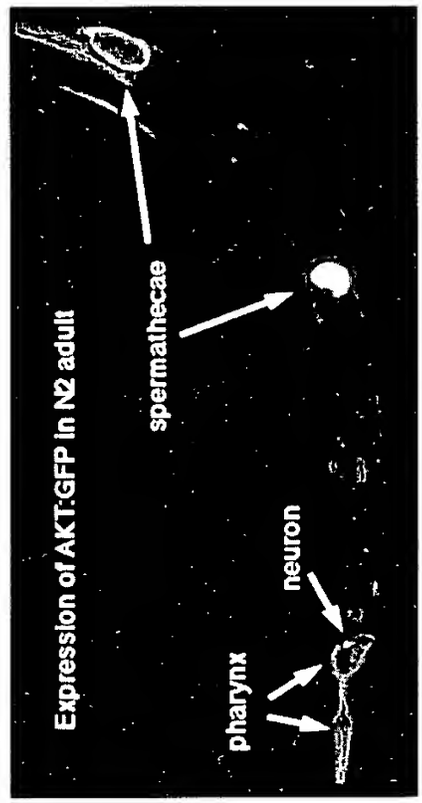
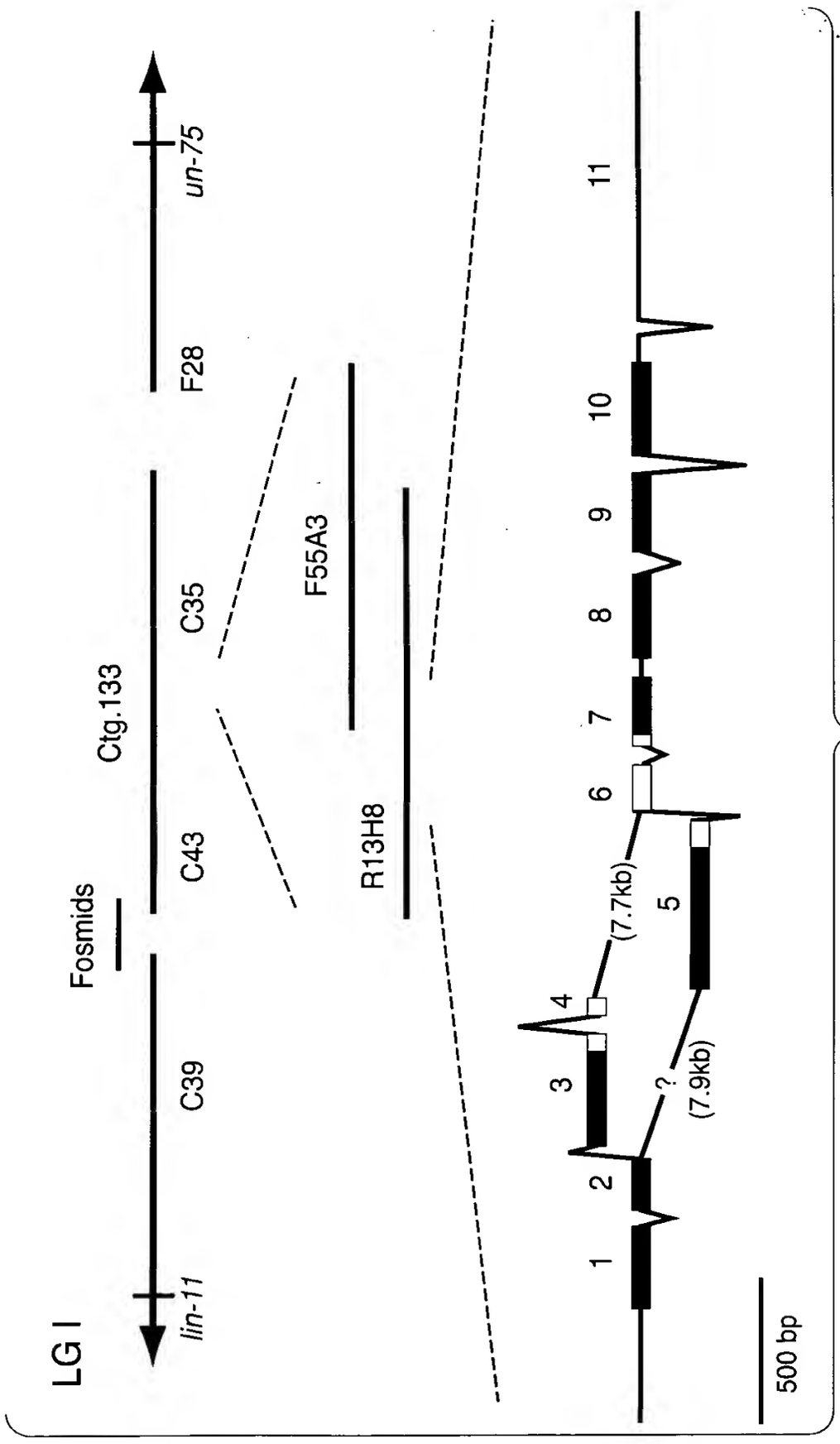


Fig. 26B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un-75
Fosmids
Ctg.133
C39
C43
C35
F28
F55A3
R13H8
1
2
3
4
5
6
7
8
9
10
11
(7.7kb)
?
(7.9kb)
500 bp

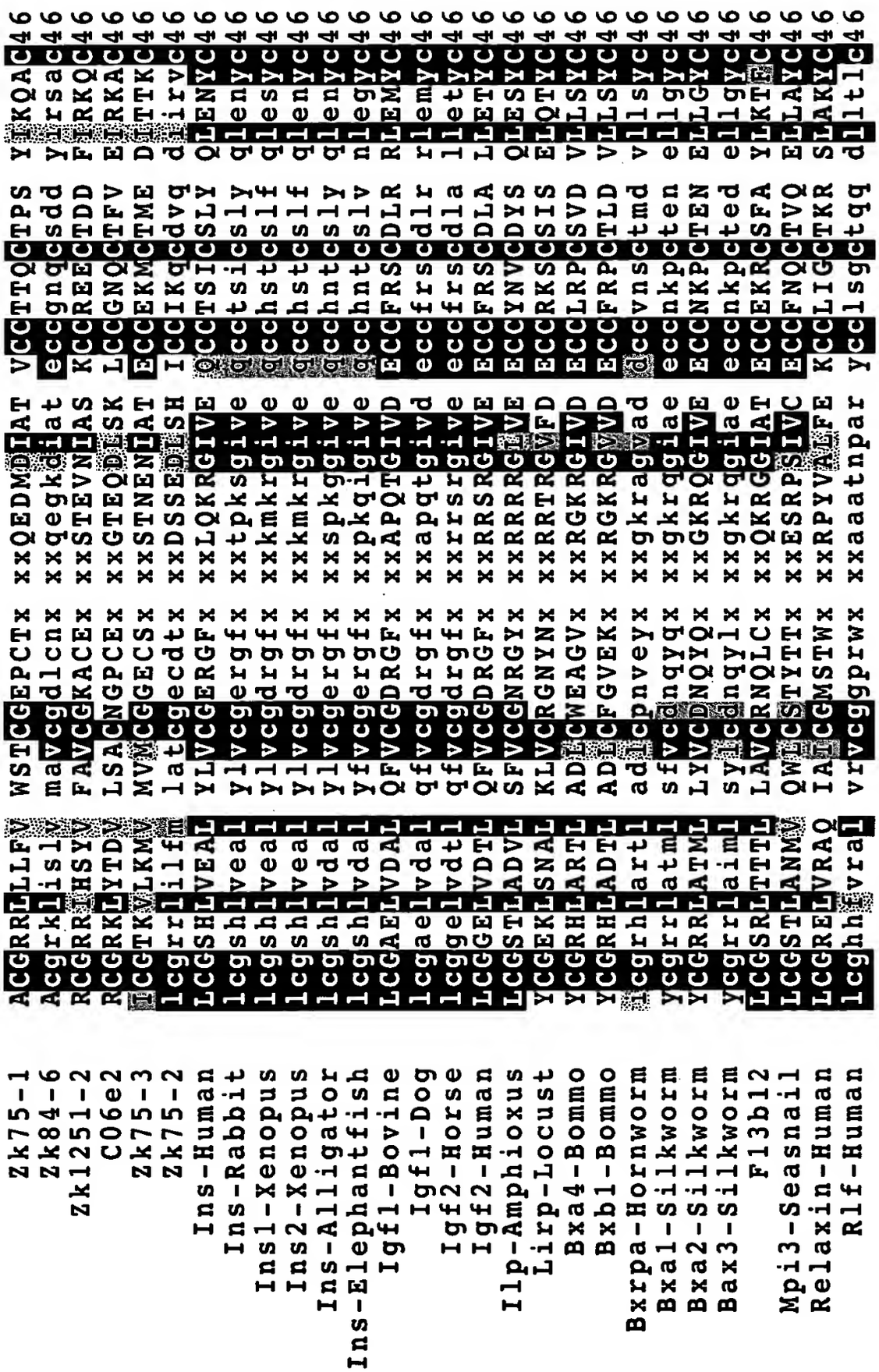
Fig. 27

```
            1               15 16              30 31              45 46              60
1 ZK84.6    -MNSVFTIIFVLCAL QVAASFRQSFG---P SMSEESASMQLLREL QH--NMMESAHRPMP  54
2 ZK75.1    -MFSFFT-YFLLSAL LLSASCRQ------P SMDT-SKADRILREI E----METELENQLS  47
3 ZK1251.2  ----MPPIILVFFLV LIPASQQY------P FSLE-SLNDQIINEE VI--EYMLENSIRSS  47
4 C06E2     --MIVTLIVFLVIGL QMAHLSQVSGNNENG FLNP-FDLSQWSEEI LHRQYHHHHHHHHGN  57
5 ZK75.2    ----MNAIIFCLLFT TVTATYEVF-----G KGIEHRNEHLIINQL D---IIPVESTPTPN  48
6 ZK75.3    MKLSVVLALFIIFQL GAASLMRN------W MFDFEKELEHDYDDS E---IGFHNIHSLMA  51
7 C17C3     --------------- --------------- ---------MKLLHI F---IIFLLFQSCSN  18
8 F13B12    --------------- --------------- ----MYWFRQVYRPS FF--FGFLAILLLSS  50
9 INSULIN   --------------- --------------- ------------MA LWMRLLPLLALLALW  17
CONSENSUS   --------------- --------------- --------------- ---------------

            61              75 76              90 91             105 106             120
1 ZK84.6    RARRVPAPGETRACG RKLISLVMAVCGD-L CN---------------- ----------------  85
2 ZK75.1    RARRVPA-GEVRACG RRLLLFVWSTCGE-P CT---------------- ----------------  77
3 ZK1251.2  RTRRVPDEKKIYRCG RRIHSYVFAVCGK-A CE---------------- ----------------  78
4 C06E2     RARRTLETEKIYRCG RKLYTDVLSACNG-P CE---------------- ----------------  88
5 ZK75.2    RASRVQK----RLCG RRLILFMLATCG--E CD---------------- ----------------  74
6 ZK75.3    RSRRGDK---VKICG TKVLKMVMVMCGG-E CS---------------- ----------------  79
7 C17C3     KMCQYSK-KKYKICG VRALKHMKVYCTR-G MT---------------- ----------------  48
8 F13B12     PTPSDAS---IRLCG SRLTTTLLAVCRNQL CTGLTAFKRSADQSY APTTRDLFHIHHQQ-   80
9 INSULIN   GPDPAAAFVNQHLCG SHLVEALYLVCGERG FFYTPKTRREAEDLQ VGQVELGGGPGAGSL   77
CONSENSUS   ----------CG ----------C---- ---------------- ----------------
                                 B CHAIN                          C PEPTIDE

            121             135 136             150 151       165 166             180
1 ZK84.6    -------PQEGKDIA TECCGNQCSDDYIRS ACCP-----    112
2 ZK75.1    -------PQEDMDIA TVCCTTQCTPSYIKQ ACCPEK---    106
3 ZK1251.2  -------SNTEVNIA SKCCREECTDDFIRK QCCP-----    105
4 C06E2     -------PGTEQDLS KLCCGNQCTFVEIRK ACCADKL--    118
5 ZK75.2    -------TDSSEDLS HICCIKQCDVQDIIR VCCPNSFRK    106
6 ZK75.3    -------S-TNENIA TECCEKMCTMEDITT KCCPSR---    107
7 C17C3     -------R-DYGKLL VTCCSKGCNAIDIQR ICL------     73
8 F13B12    ---------KRGGIA TECCEKRCSFAYLKT FCCNQDDN-    109
9 INSULIN   QPLALEGSLQKRGIV EQCCTSICSLYQLEN YCN-------    110
CONSENSUS   ----------------CC---C------- --C-------
                                 A CHAIN
```

Fig. 28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zk1251-2
C06e2
Zk75-3
Zk75-2
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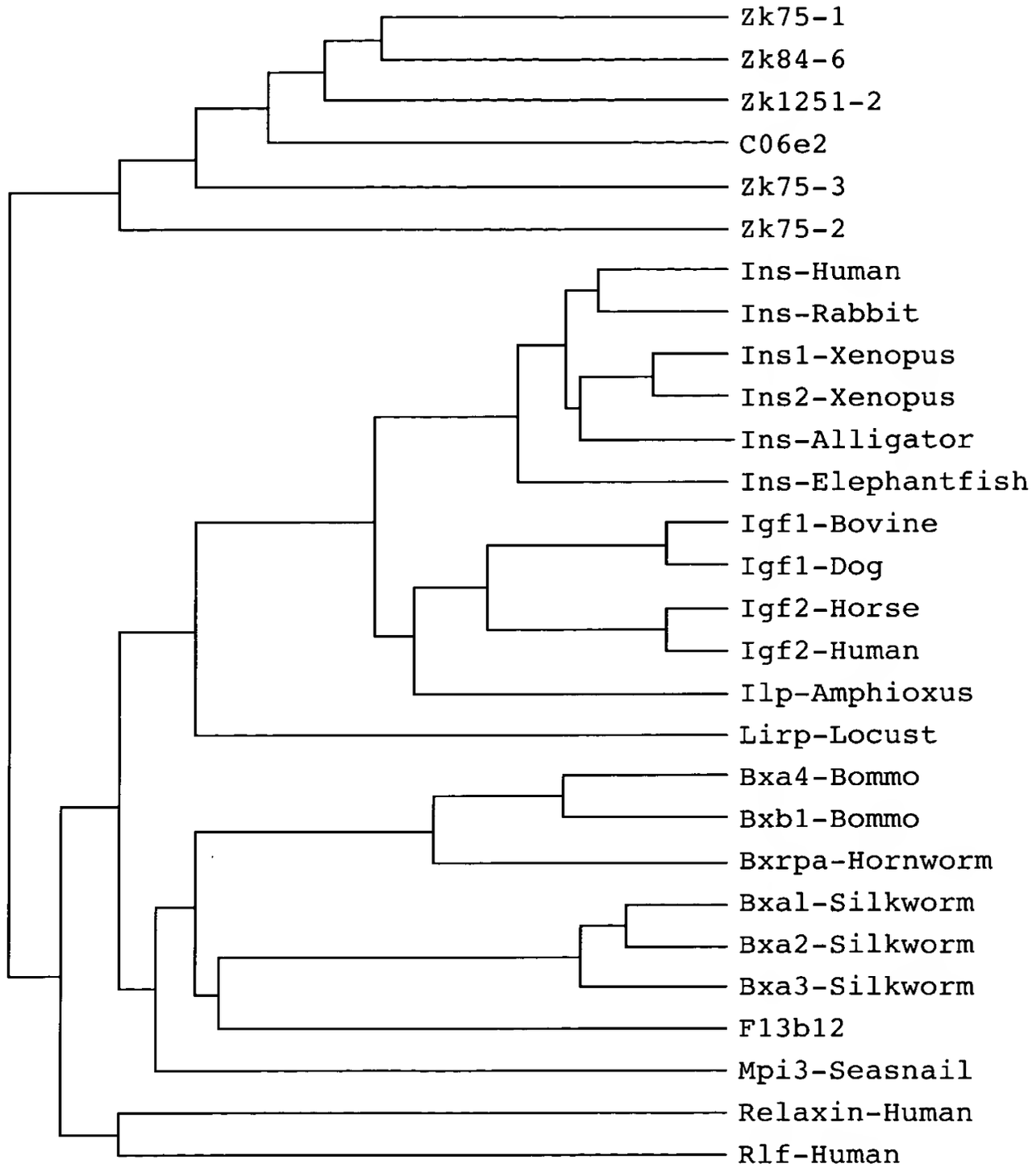
Ins-Rabbit
Ins1-Xenopus
Ins2-Xenopus
Ins-Alligator
Ins-Elephantfish
Igf1-Bovine
Igf1-Dog
Igf2-Horse
Igf2-Human
Ilp-Amphioxus
Lirp-Locust
Bxa4-Bommo
Bxb1-Bommo
Bxrpa-Hornworm
Bxa1-Silkworm
Bxa2-Silkworm
Bax3-Silkworm
F13b12
Mpi3-Seasnail
Relaxin-Human
Rlf-Human

Fig. 29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C06e2
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Zk75-2
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Ins-Rabbit
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Ins2-Xenopus
Ins-Alligator
Ins-Elephantfish
Igf1-Bovine
Igf1-Dog
Igf2-Horse
Igf2-Human
Ilp-Amphioxus
Lirp-Locust
Bxa4-Bommo
Bxb1-Bommo
Bxrpa-Hornworm
Bxa1-Silkworm
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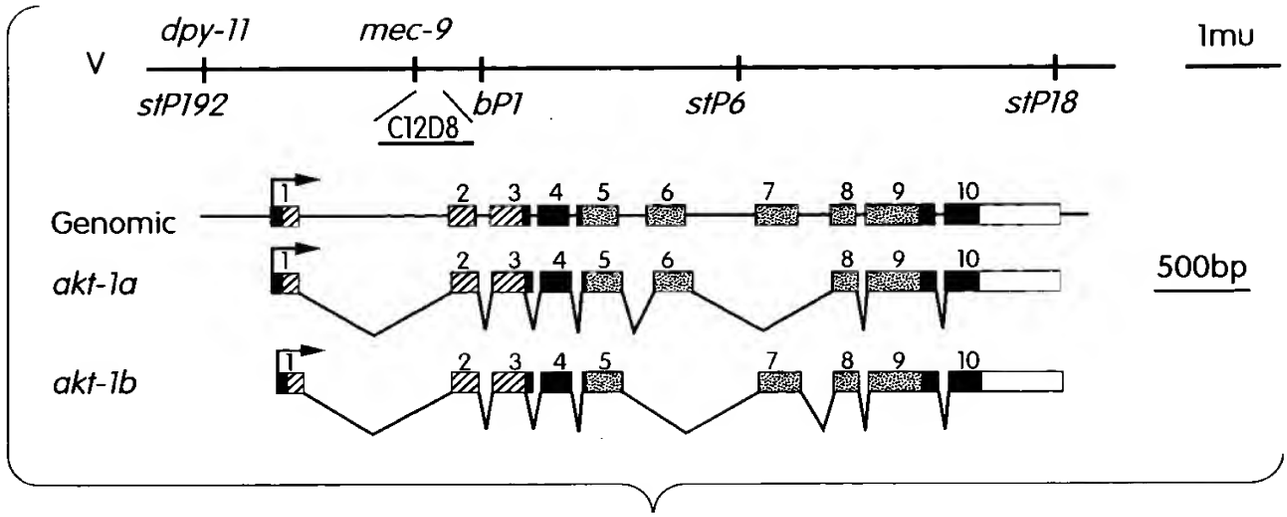
Bxa3-Silkworm
F13b12
Mpi3-Seasnail
Relaxin-Human
Rlf-Human

Fig. 30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500bp

Fig. 31

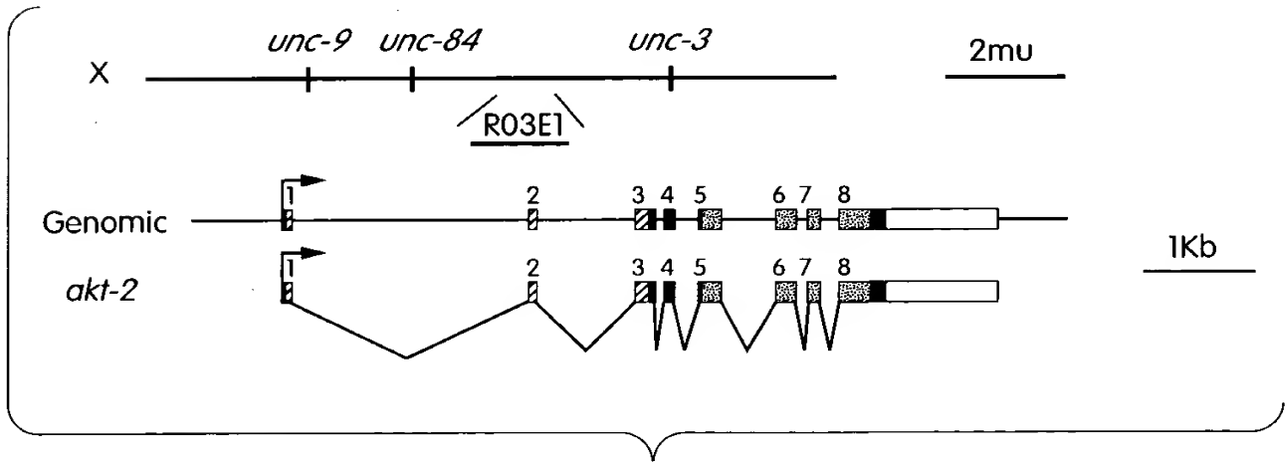
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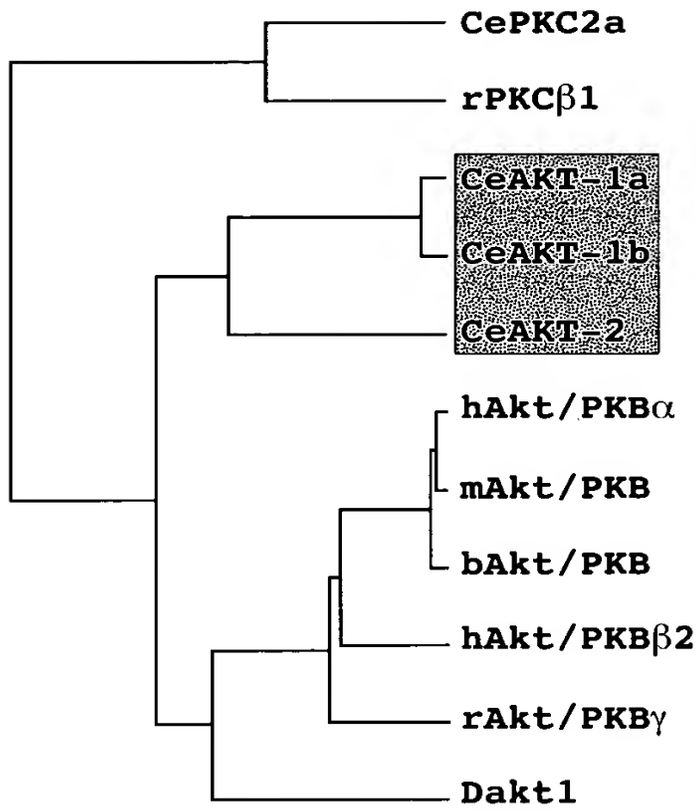
Fig. 32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Dakt1

Fig. 33

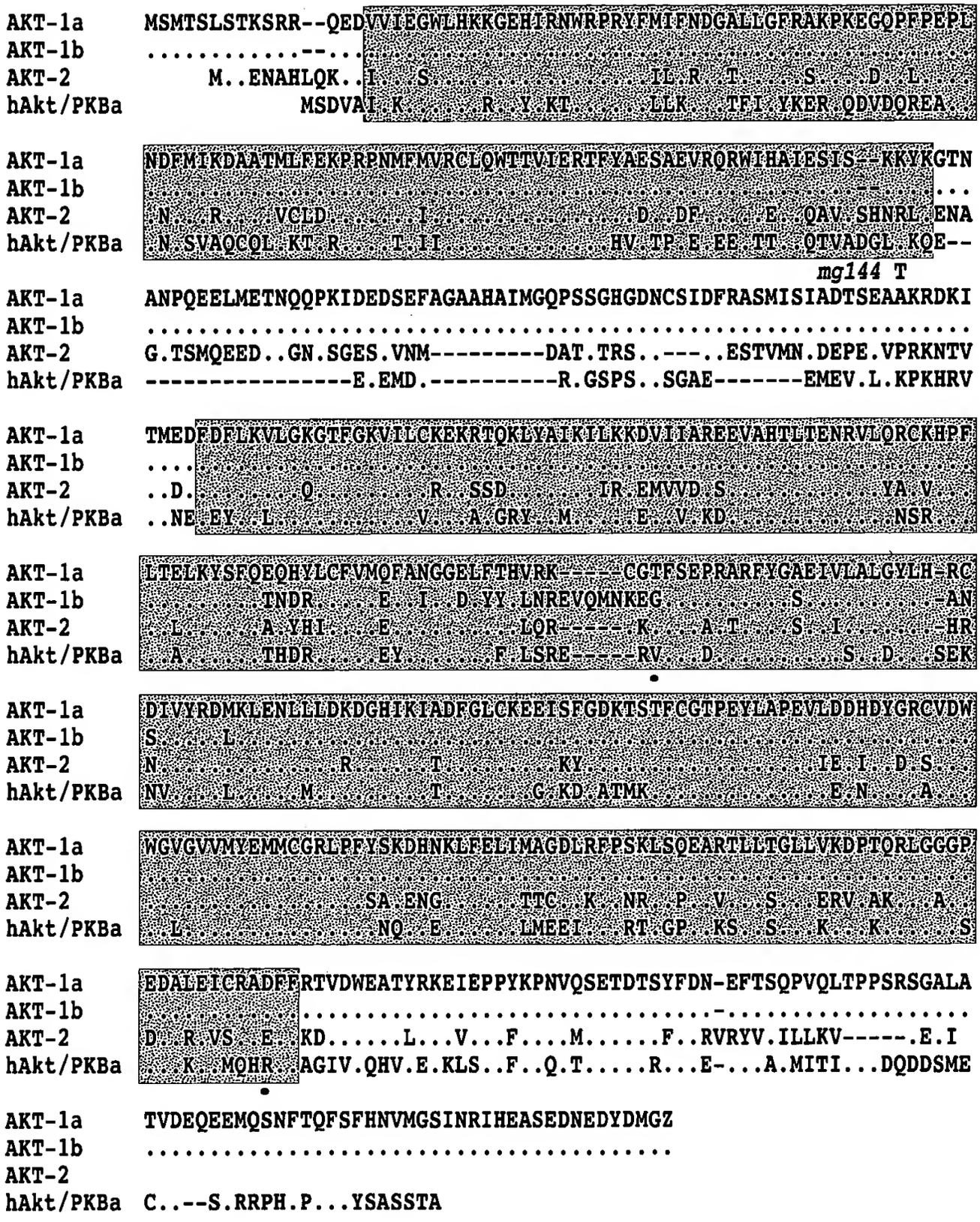

Fig. 34

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Fig. 35A

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Fig. 35B

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DANQASSRSSDSGSPPPTRFYSDEEEENTARRTTFVGTALYVSPEMLADGDVGPQTDIWGLGCILFQCLAGQPPFRAV
NQYHLLKRIQELDFSFPEGFPEEASEIIAKILVRDPSTRITSQELMAHKFFENVDWVNIANIKPPVLHAYIPATFGEP
EYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEEQRVK
NPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIHTPNR
VYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEEKKAL
KAEQVSKKLSMQMDKKSP

Fig. 36

MEDLTPTNTSLDTTTTNNDTTSDREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
AYSQVFRCREVATDAMFAVKVLQKSYLNRHQKMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
DANQASSRSSDSGSPPPTRFYSDEEVPEENTARRTTFVGTALYVSPEMLADGDVGPQTDIWGLGCILFQCLAGQPPFR
AVNQYHLLKRIQELDFSFPEGFPEEASEIIAKILVRDPSTRITSQELMAHKFFENVDWVNIANIKPPVLHAYIPATF
GEPEYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTFRPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEE
QRVKNPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIH
TPNRVYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEE
KKALKAEQVSKKLSMQMDKKSP

Fig. 37

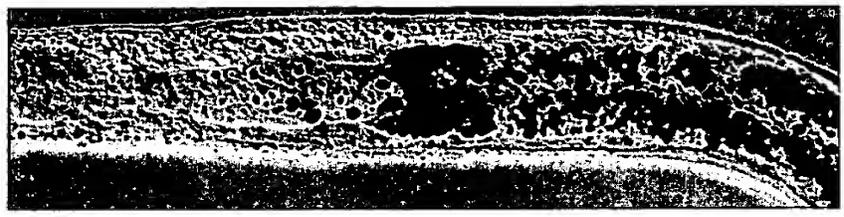

Fig. 38A

Fig. 38B

Fig. 38C

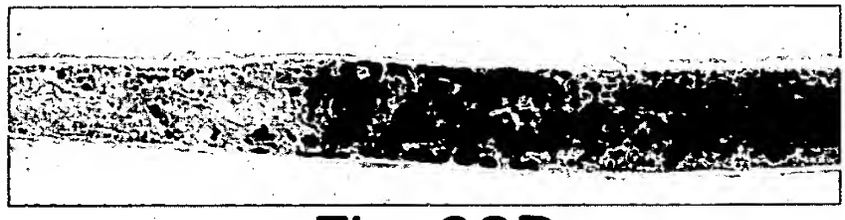

Fig. 38D

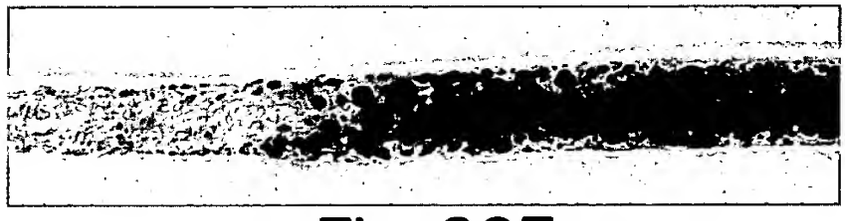

Fig. 38E

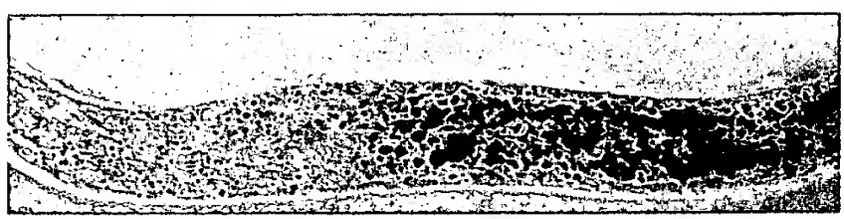

Fig. 38F

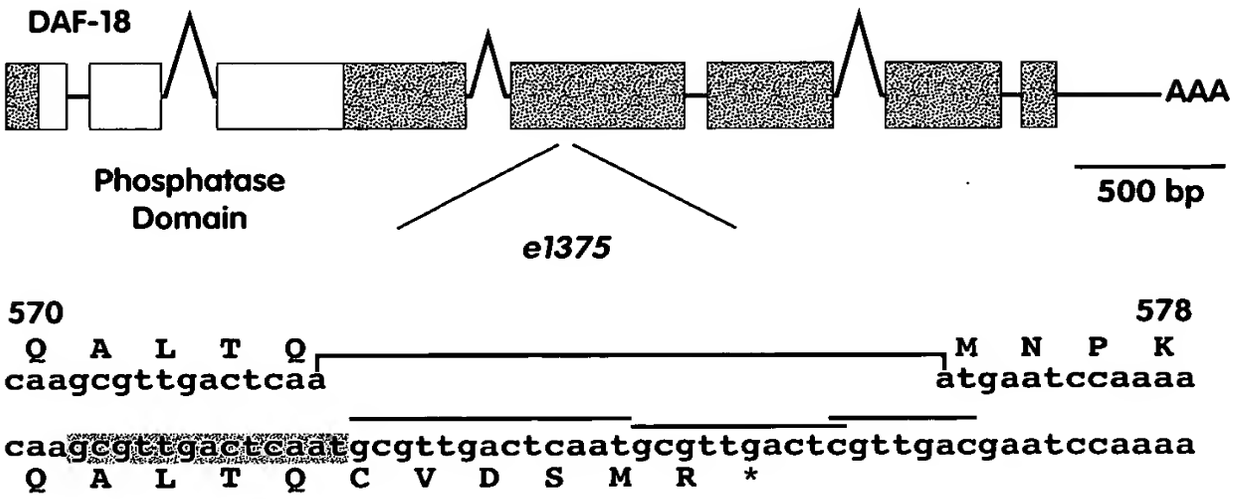

Fig. 39A

```
DAF-18   48 IFRTAVSSNR CRTEYQNIDL DCAYITDRII AIGYPAIGIE ANFRNSKVQT
PTEN      4 IIKEIVSRNK RRYQEDGFDL DLTYIYPNII AMGFPAERLE GVYRNNIDDV

DAF-18   98 QQFLTRRHGK GNVKVFNLRG GYYYDADNFD GNVICFDMTD HHPPSLELMA
PTEN     54 VRFLDSKH.K NHYKIYNLCA ERHYDTAKFN CRVAQYPFED HNPPQLELIK

DAF-18  148 PFCREAKEWL EADDKHVIAV HCKAGKGRTG VMICALLIYI NFYPSPRQIL
PTEN    103 PFCEDLDQWL SEDDNHVAAI HCKAGKGRTG VMICAYLLHR GKFLKAQEAL

DAF-18  198 DYYSIIRTKN NKGVTIPSQR RYIYYYHKLR ERELNYLPLR MQLIGVYVER
PTEN    153 DFYGEVRTRD KKGVTIPSQR RYVYYYSYLL KNHLDYRPVA LLFHKMMFET

DAF-18  248 PPKTWGGGSK IKVEVGNGST ILFKPD..PL IISKSNHQRE RATWLNNCDT
PTEN    203 IPMFSGGTCN PQFVVCQLKV KIYSSNSGPT RREDKFMYFE FPQPLPVCGD
```

Fig. 39B

DAF-18 Protein

MVTPPPDVPSTSTRSMARDLQENPNRQPGEPRVSEPYHNSIVERIRHIFRTAVSSNRCRTEYQNIDLDCAYITDRIIAIG
YPATGIEANFRNSKVQTQQFLTRRHGKGNVKVFNLRGGYYYDADNFDGNVICFDMTDHHPPSLELMAPFCREAKEWLEAD
DKHVIAVHCKAGKGRTGVMICALLIYINFYPSPRQILDYYSIIRTKNNKGVTIPSQRRYIYYYHKLRERELNYLPLRMQL
IGVYVERPPKTWGGGSKIKVEVGNGSTILFKPDPLIISKSNHQRERATWLNNCDTPNEFDTGEQKYHGFVSKRAYCFMVP
EDAPVFVEGDVRIDIREIGFLKKFSDGKIGHVWFNTMFACDGGLNGGHFEYVDKTQPYIGDDTSIGRKNGMRRNETPMRK
IDPETGNEFESPWQIVNPPGLEKHITEEQAMENYTNYGMIPPRYTISKILHEKHEKGIVKDDYNDRKLPMGDKSYTESGK
SGDIRGVGGPFEIPYKAEEHVLTFPVYEMDRALKSKDLNNGMKLHVVLRCVDTRDSKMMEKSEVFGNLAFHNESTRRLQA
LTQMNPKWRPEPCAFGSKGAEMHYPPSVRYSSNDGKYNGACSENLVSDFFEHRNIAVLNRYCRYFYKQRSTSRSRYPRKF
RYCPLIKKHFYIPADTDDVDENGQPFFHSPEHYIKEQEKIDAEKAAKGIENTGPSTSGSSAPGTIKKTEASQSDKVKPAT
EDELPPARLPDNVRRFPVVGVDFENPEEESCEHKTVESIAGFEPLEHLFHESYHPNTAGNMLRQDYHTDSEVKIAEQEAK
AFVDQLLNGQGVLQEFMKQFKVPSDNSFADYVTGQAEVFKAQIALLEQSEDFQRVQANAEEVDLEHTLGEAFERFGHVVE
ESNGSSKNPKALKTREQMVKETGKDTQKTRNHVLLHLEANHRVQIERRETCPELHPEDKIPRIAHFSENSFSDSNFDQAI
YL

Fig. 40A

```
   1 ttccaggtac atctactaac ccccaatggt tactcctcct ccagatgtgc caagcacatc
  61 gaccaggtcg atggctcgtg accttcaaga gaatccaaac cgacaacctg gtgaaccacg
 121 tgtgtctgaa ccgtatcaca attcaatcgt cgagcggatt cgccatattt ttcggacggc
 181 tgtatcttcc aatcgttgtc gcaccgagta ccaaaatatc gacctagatt gtgcatatat
 241 cacagaccga atcatagcta tcggttatcc agcaacagga atcgaagcga atttccgtaa
 301 ctcaaaagtt caaactcaac aatttctgac caggcggcac ggaaagggca acgtgaaggt
 361 gtttaacctg cgcggtggat actactacga tgcggataac ttcgatggaa atgttatttg
 421 cttcgatatg actgatcatc atccgccgag tctcgaatta atggctccgt tttgcagaga
 481 ggctaaggaa tggcttgaag cagacgataa acatgtaata gctgtacact gtaaagctgg
 541 aaaaggccgt accggagtga tgatatgtgc tcttctcatc tacatcaact tctatccgag
 601 cccacgacaa attctcgact actactcaat aattcgtaca aaaaacaaca aaggtgtcac
 661 aattccatca caacgacgct acatttacta ctaccataag cttcgtgaac gtgagctcaa
 721 ctatttacca ttgagaatgc agttgattgg tgtctacgtg gaacggcctc caaagacatg
 781 gggtggtggt tcaaagataa aagtggaggt tggaaatggc tcgacaattt tatttaagcc
 841 ggatcctctc ataatctcca aatcaaatca tcagcgagag cgtgcgacgt ggctgaacaa
 901 ctgtgatacg cctaacgaat tcgacaccgg agagcaaaaa tatcatggat ttgtttccaa
 961 gagagcatac tgttttatgg tgccagaaga tgctccagta tttgtcgaag gagatgttcg
1021 tatagacatt cgcgaaatcg gatttctcaa aaagttttcg gacgggaaga ttggtcatgt
1081 ttggttcaat acaatgttcg catgtgatgg aggactcaac ggtggacatt tcgagtacgt
1141 agacaaaact cagccgtaca tcggagacga tacatcaatc ggacggaaaa atggaatgcg
1201 aagaaatgaa acgccgatgc gaaaaattga tccagaaact ggaaatgaat ttgagtctcc
1261 gtggcaaata gtgaatcctc ctggactgga aaaacatatt acggaggaac aagcaatgga
1321 aaattatacc aattatggca tgattcctcc tcgatacacg atcagcaaga ttcttcacga
1381 aaagcatgaa aaaggtatcg tcaaggatga ctataatgat cgtaagctgc caatgggaga
1441 caaatcatac acggaatcag gaaaaagtgg agatattcga ggagtcggtg gtccatttga
1501 gataccatat aaagctgagg aacatgttct cacatttcca gtttatgaaa tggatcgagc
1561 attgaagagt aaagatctta acaacggaat gaaacttcac gttgttcttc gttgtgtaga
1621 tactcgtgat tcaaaaatga tggaaaagag cgaagtgttc ggcaatctgg cattccataa
1681 tgaatcgaca cggaggcttc aagcgttgac tcaaatgaat ccaaaatggc gacctgaacc
1741 gtgtgcgttc ggatccaaag gtgctgaaat gcattaccct ccgtcggttc gatattcaag
1801 caatgatgga aagtataatg gagcctgcag tgagaacctt gttagcgatt ttttcgagca
1861 cagaaatatt gccgttctta atcgatattg ccgatatttc tacaagcaac gcagtacatc
1921 tcgaagccgt tatccaagaa aattcagata ctgtcctctg atcaagaaac atttctacat
1981 tccagctgat accgatgatg ttgatgaaaa tgggcaaccg ttcttccact caccagagca
2041 ttacattaaa gaacaggaaa aaatagacgc agagaaagca gctaaaggaa ttgaaaatac
2101 tggacccagt acttcaggat caagtgctcc cggaactatc aagaaaacgg aagcttcaca
2161 atccgacaag gtgaagccgg caactgaaga cgaacttcct cctgcgaggc taccggataa
2221 tgtgcgaaga tttccagtcg tcggcgttga tttcgaaaat ccggaagaag aatcgtgtga
2281 acacaaaacc gtagagtcaa tagctggttt tgaaccactc gaacatctat tccatgaatc
2341 ataccatcca aatacggccg gtaacatgct gcgtcaggat tatcacactg attcggaagt
2401 gaaaatagct gaacaagagg caaaagcctt cgttgaccag ttgcttaatg gacaaggtgt
2461 attacaagag tttatgaagc aattcaaagt accatcggac aattcctttg ctgattatgt
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Fig. 40B (sheet 1 of 2)

```
2521 aaccggacag gccgaagttt ttaaagcaca gattgcgtta ctggagcagt cggaggattt
2581 tcaacgagtt caagcgaatg cagaggaagt cgatcttgaa cacactcttg gtgaagcgtt
2641 tgagcgattc gggcacgttg tagaagaatc gaatggttct tctaaaaatc caaaagccct
2701 gaaaactcga gaacaaatgg tgaaagaaac tggcaaagac actcagaaga cccgcaatca
2761 tgtgcttcta catttggaag ctaatcatcg tgtgcaaatc gagcgtcgtg aaacgtgccc
2821 ggagctacat ccagaggata aaatcccaag aattgctcat ttttccgaaa acagcttctc
2881 ggattcgaat tttgatcaag ctatttattt gtaaacctaa aacaaaactt ttagaagatt
2941 ttcttcttac tgaccctcca attttcagat aatttcaatg ttttaagttt tctcttcaaa
3001 gtatcattca ctttctgtat agtgttttgt tttttaacaa actattgttc gattattttg
3061 tatattcata ttatagctct caacttcccg attttccacg tatatatgta tattttgccg
3121 ggtgaaaaat agcaattccc tatgaatgta tccccttcca tctgttttct tactcagaaa
3181 ttgtaattca cattgcgggt catcactaat cctatgggct ttaacacaat tctcccataa
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3301 ataa
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Fig. 40B (sheet 2 of 2)

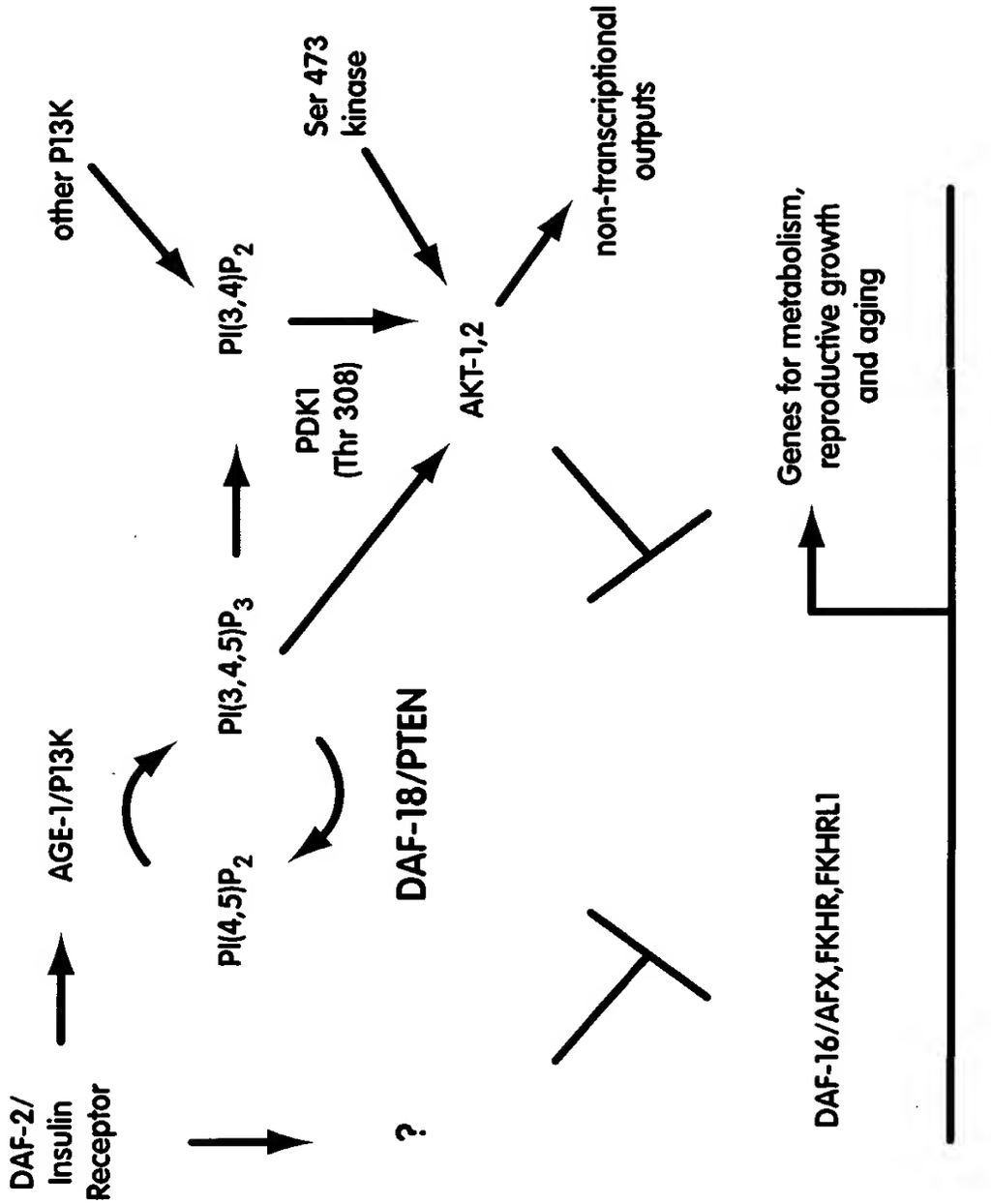

Fig. 41

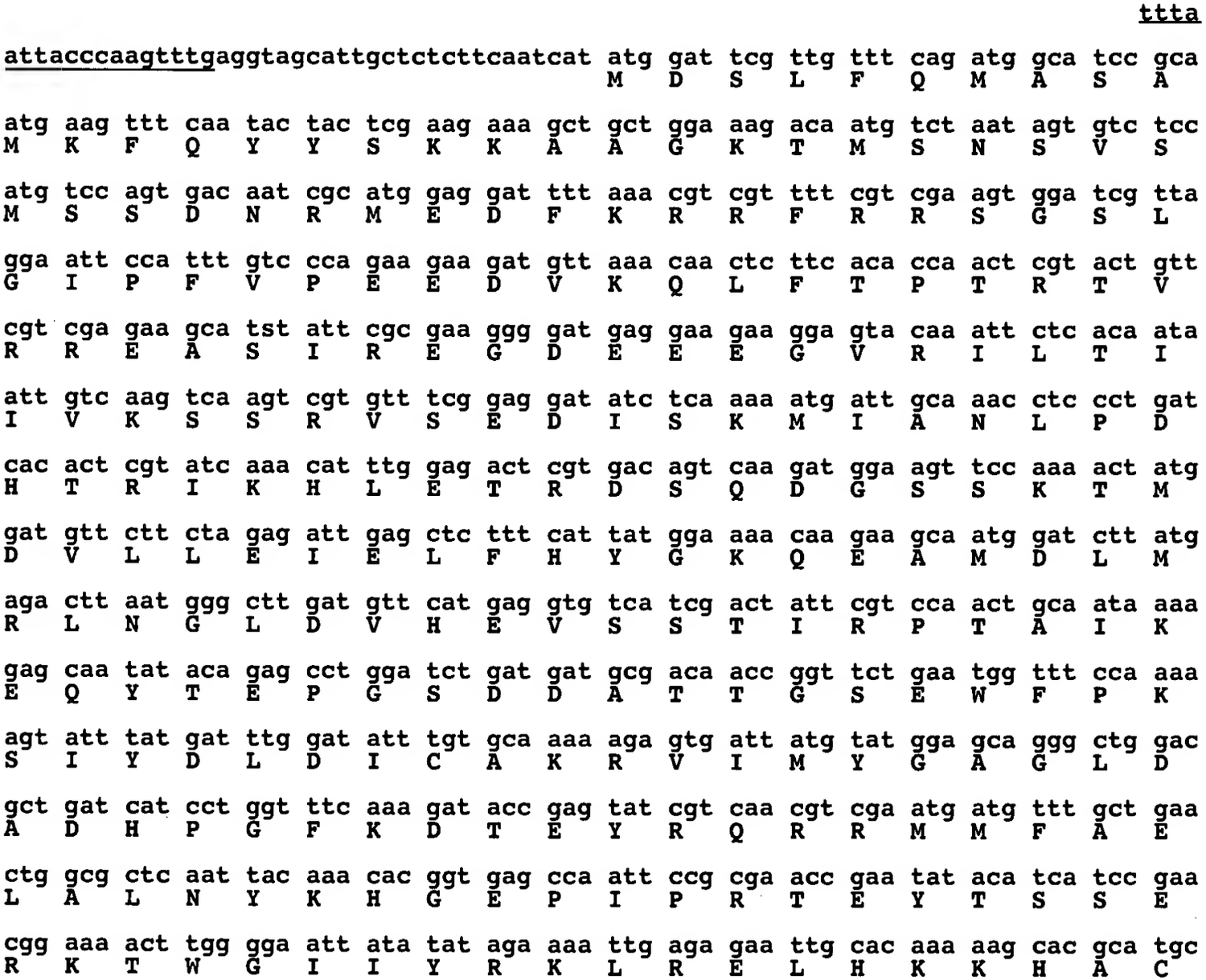

Fig. 42 (sheet 1 of 2)

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att ccg caa cta gaa gat atc tgc aag ttt ttg aaa gca aaa act gga ttc cgt gtt cgc
I   P   Q   L   E   D   I   C   K   F   L   K   A   K   T   G   F   R   V   R

cca gtc gcc gga tac tta tca gct cgt gat ttc ttg gca ggt ctt gca tat cgt gtc ttc
P   V   A   G   Y   L   S   A   R   D   F   L   A   G   L   A   Y   R   V   F

ttc tgc act caa tac gtt cgc cat cat gcc gat cca ttt tac act cca gaa cca gac acc
F   C   T   Q   Y   V   R   H   H   A   D   P   F   Y   T   P   E   P   D   T

gtt cac gag ctc atg ggt cac atg gct cta ttc gct gat cca gat ttt gct cag ttt tct
V   H   E   L   M   G   H   M   A   L   F   A   D   P   D   F   A   Q   F   S

caa gag att gga tta gct tct ctt gga gca tca gag gaa gat ttg aag aag ctt gca aca
Q   E   I   G   L   A   S   L   G   A   S   E   E   D   L   K   K   L   A   T

ctc tac ttc ttt tcc att gaa ttt ggt ctc tcg tct gat gac gct gcc gat tct cca gta
L   Y   F   F   S   I   E   F   G   L   S   S   D   D   A   A   D   S   P   V

aaa gaa aat gga tca aat cat gaa aga ttt aaa gta tac gga gca gga ctt ctg agc agt
K   E   N   G   S   N   H   E   R   F   K   V   Y   G   A   G   L   L   S   S

gct ggc gag ttg caa cat gcc gtt gag ggt agt gca acc att att cgt ttt gat ccg gat
A   G   E   L   Q   H   A   V   E   G   S   A   T   I   I   R   F   D   P   D

cgt gtt gtt gag caa gaa tgt ctc att act act ttc cag tca gcg tat ttc tat act aga
R   V   V   E   Q   E   C   L   I   T   T   F   Q   S   A   Y   F   Y   T   R

aat ttt gaa gag gcc cag cag aaa ctc aga atg ttc acc aac aac atg aaa cgt ccc ttc
N   F   E   E   A   Q   Q   K   L   R   M   F   T   N   N   M   K   R   P   F

att gtt cgt tac aac cca tac aca gaa agc gtc gaa gtt ctc aac aac tcc cgt tcc att
I   V   R   Y   N   P   Y   T   E   S   V   E   V   L   N   N   S   R   S   I

atg ttg gca gtg aac tct ctc cgc tca gac atc aac ctg ctc gcc gga gct ctc cac tac
M   L   A   V   N   S   L   R   S   D   I   N   L   L   A   G   A   L   H   Y

atc ctg tag
I   L   *
```

Fig. 42 (sheet 2 of 2)

```
                                                        attacccaagtttgaggtagcattgctctcttcaatcat
atg gat tcg ttg ttt cag atg gca tcc gca atg aag ttt caa tac tac tcg aag aaa gct
M   D   S   L   F   Q   M   A   S   A   M   K   F   Q   Y   Y   S   K   K   A

gct gga aag aca atg tct aat agt gtc aaa aac tgg att ccg tgt tcg ccc agt cgc cgg
A   G   K   T   M   S   N   S   V   K   N   W   I   P   C   S   P   S   R   R

ata ctt atc agc tcg tga ttt ctt ggc agg tct tgc ata tcg tgt ctt ctt ctg cac tca
I   L   I   S   S   *

ata cgt tcg cca tca tgc cga tcc att tta cac tcc aga acc aga cac cgt tca cga gct
cat ggg·tca cat ggc tct att cgc tga tcc aga ttt tgc tca gtt ttc tca aga gat tgg
att agc ttc tct tgg agc atc aga gga aga ttt gaa gaa gct tgc aac act cta ctt ctt
ttc cat tga att tgg tct ctc gtc tga tga cgc tgc cga ttc tcc agt aaa aga aaa tgg
atc aaa tca tga aag att taa agt ata cgg agc agg act tct gag cag tgc tgg cga gtt
gca aca tgc cgt tga ggg tag tgc aac cat tat tcg ttt tga tcc gga tcg tgt tgt tga
gca aga atg tct cat tac tac ttt cca gtc agc gta ttt cta tac tag aaa ttt tga aga
ggc cca gca gaa act cag aat gtt cac caa caa cat gaa acg tcc ctt cat tgt tcg tta
caa ccc ata cac aga aag cgt cga agt tct caa caa ctc ccg ttc cat tat gtt ggc agt
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Fig. 43

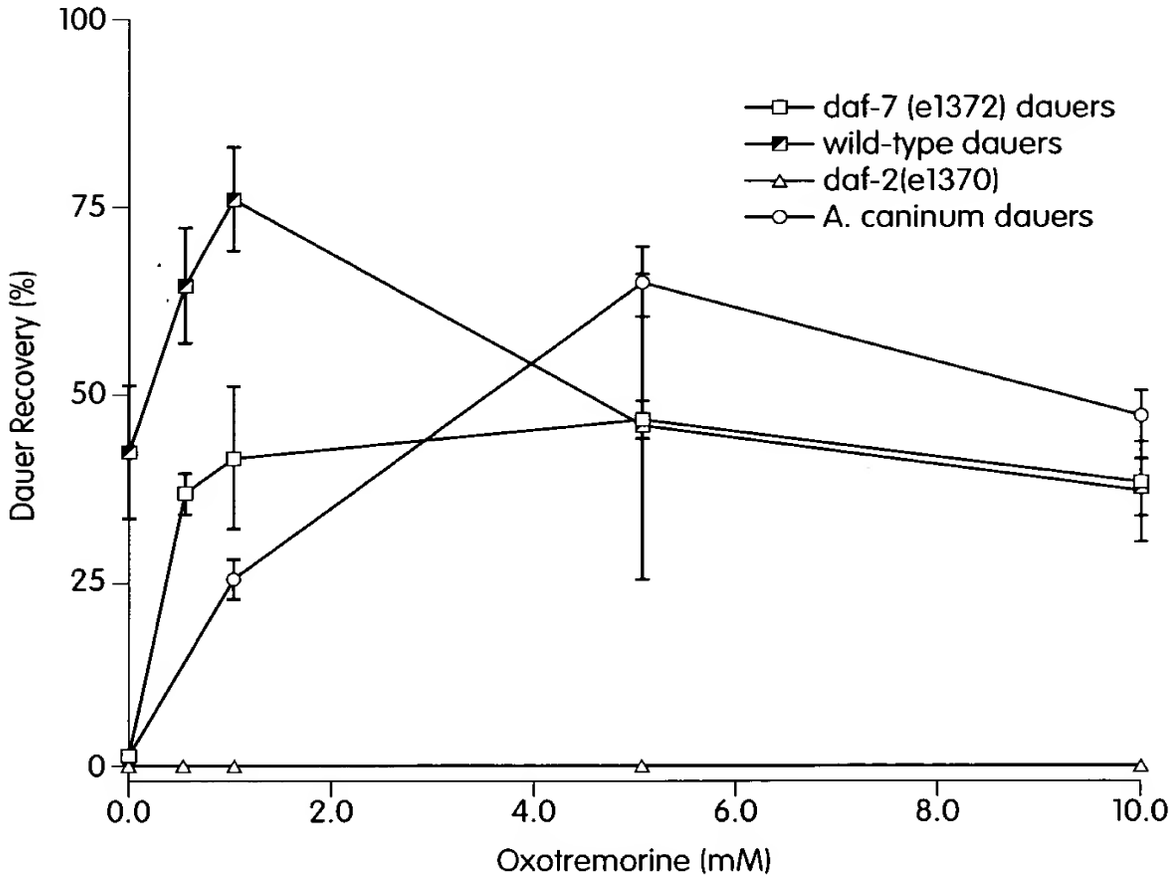
100
75
50
25
0
Dauer Recovery (%)
0.0
2.0
4.0
6.0
8.0
10.0
Oxotremorine (mM)
daf-7 (e1372) dauers
wild-type dauers
daf-2(e1370)
A. caninum dauers

Fig. 44A

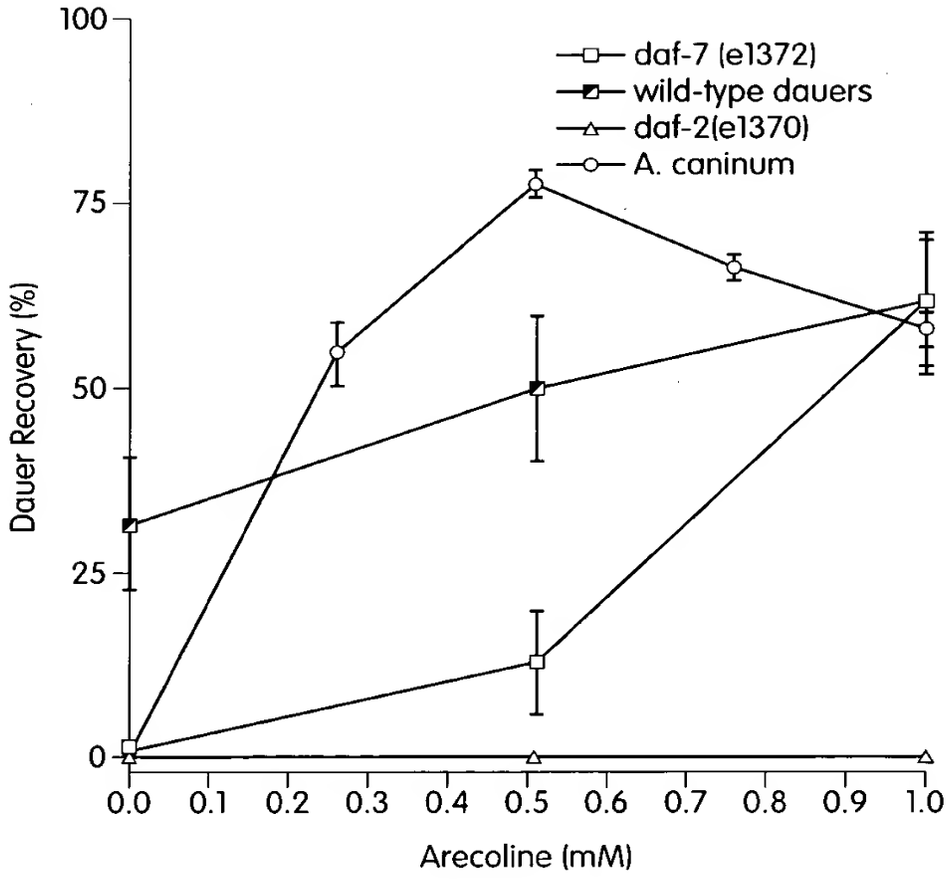
daf-7 (e1372)
wild-type dauers
daf-2(e1370)
A. caninum
Dauer Recovery (%)
100
75
50
25
0
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Arecoline (mM)

Fig. 44B

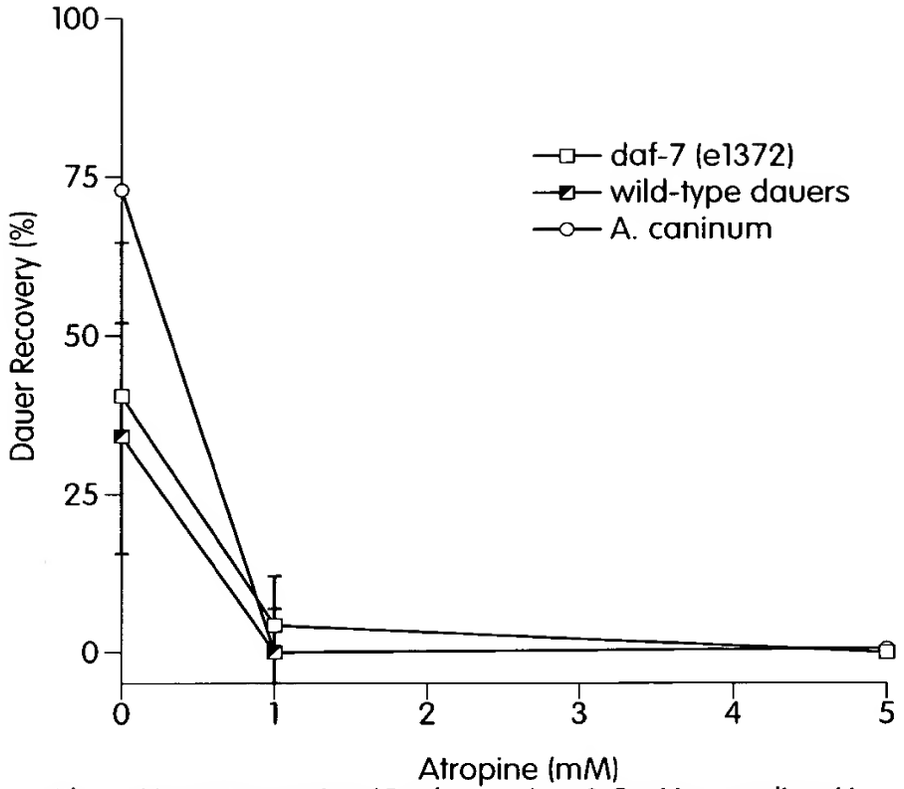
100
75
50
25
0
Dauer Recovery (%)
daf-7 (e1372)
wild-type dauers
A. caninum
0
1
2
3
4
5
Atropine (mM)
with 1mM oxotremorine (C. elegans) or 0.5mM arecoline (A. caninum)

Fig. 44C

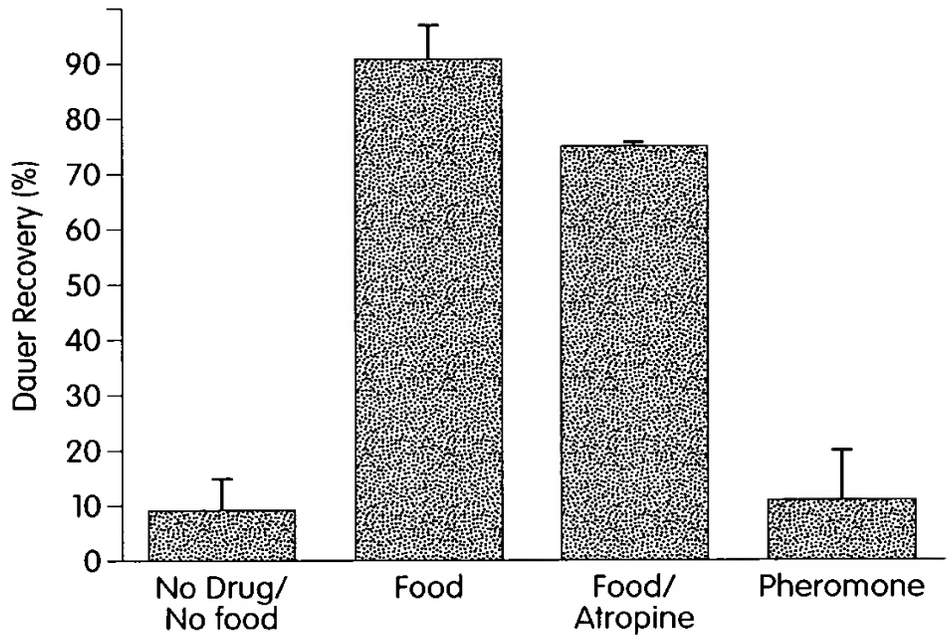
Dauer Recovery (%)
90
80
70
60
50
40
30
20
10
0
No Drug/
No food
Food
Food/
Atropine
Pheromone

Fig. 45A

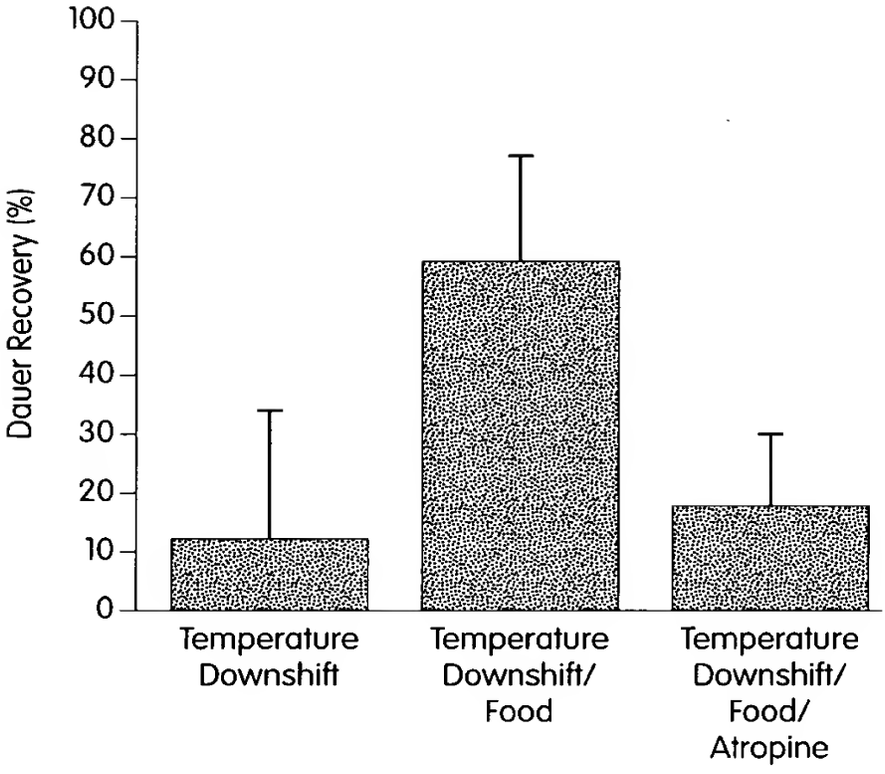
Dauer Recovery (%)
100
90
80
70
60
50
40
30
20
10
0
Temperature Downshift
Temperature Downshift/ Food
Temperature Downshift/ Food/ Atropine

Fig. 45B

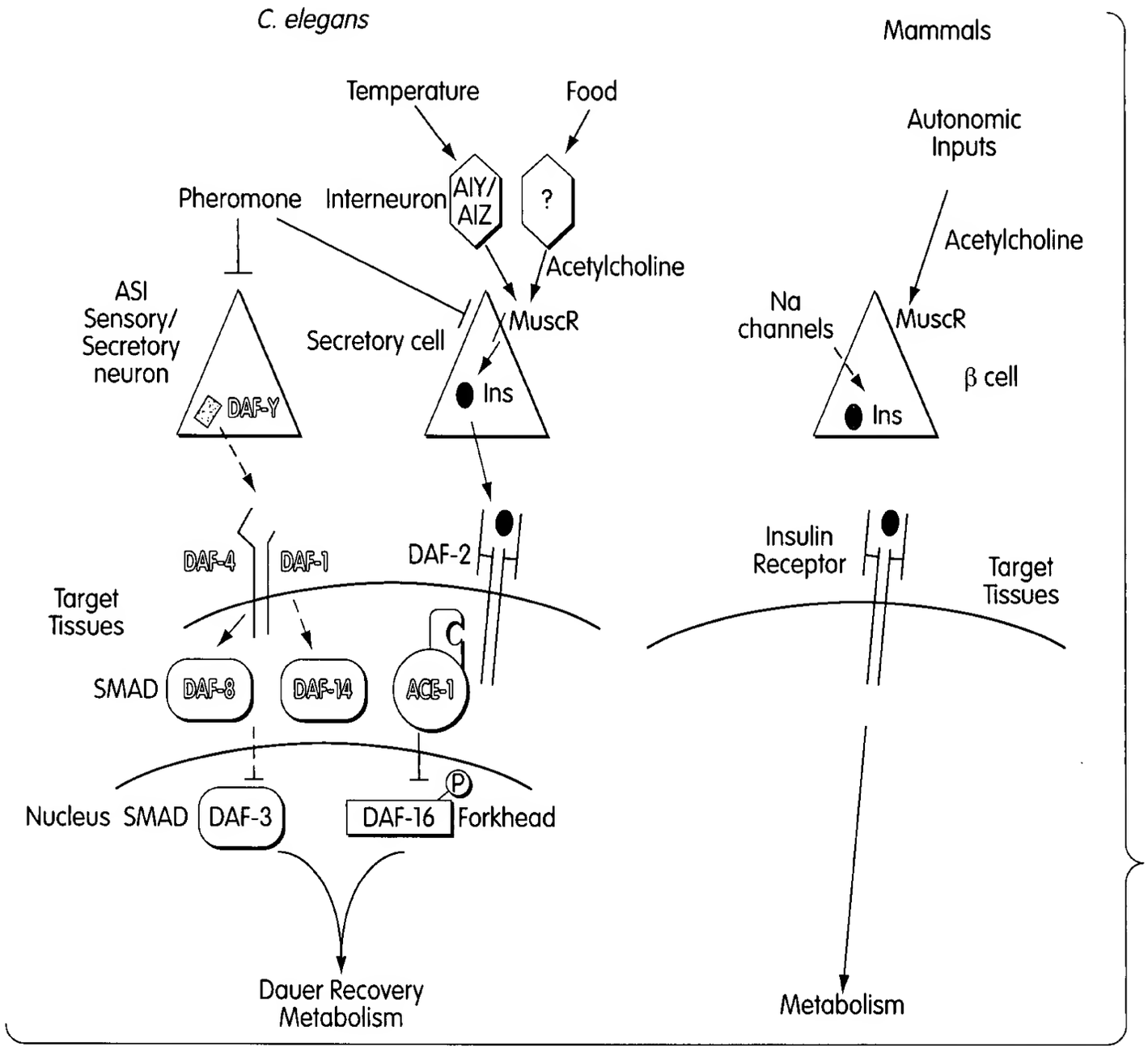
C. elegans
Mammals
Temperature
Food
Autonomic Inputs
Pheromone
Interneuron
AIY/ AIZ
?
Acetylcholine
Acetylcholine
ASI Sensory/ Secretory neuron
Secretory cell
MuscR
Na channels
MuscR
β cell
DAF-Y
Ins
Ins
DAF-4
DAF-1
DAF-2
Insulin Receptor
Target Tissues
Target Tissues
SMAD
DAF-8
DAF-14
ACE-1
C
Nucleus SMAD
DAF-3
DAF-16
P
Forkhead
Dauer Recovery Metabolism
Metabolism

Fig. 46

ATTCGGCATGAGCATGGaGCTTCGAGTCCTAGAGAACACAAAACGTTCCCGGCGGAACCTGGGtCTGGACTGCGAC
GAGACTCAAGCGAGTCCCGCTGCTGCCGATATCCCCTCACAGTGGACTTTGAGGCTTTCGGCTGGGACTGGATCAT
CGCACCTAAGCGCTACAAGGCCAACTACTGCTCCGGCCAGTGGGAGTACATGTTCATGCAAAAATATCCGCATACC
CATTTGGTGCAGCAGGCCAATCCAAGAGGTTATGcTGGGCCCTGTTGTACCCCCACCAAGATGTCCCCAATcAACA
TgcTctACTTCAATGACAAGCAGCAGATTATcTACGGCAAGATCCCTGGCATGGTGGTGGATCGCTGTGGcTGCTC
TTAAGGTGGGGGATAGAGGATGCCTCCCCCACAGACCGTACCCCAAGACCCATAGCCcTGCCCAATCCACCGCCTG
ATCCAAACAT

Fig. 47A

IRHEHGASSPREHKTFPAEPGSGLRRDSSESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQWEYMFMQKYPHT
HLVQQANPRGYAGPCCTPTKMSPINMLYFNDKQQIIYGKIPLAMVVDRCGCS

Fig. 47B